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Apelin as A Novel Biomarker in Gestational Diabetes Prediction, Prognosis, and Treatment: A Review article

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ABSTRACT

Gestational diabetes mellitus (GDM) is a prevalent health disorder that affects pregnant women with no prior history of DM at 24-28 weeks of gestation. It inversely impacts feto-maternal well-being and represents an important cause of raised morbidity and mortality. For that, earlier screening for GDM is crucial to reduce these adverse outcomes. Traditional screening methods are hindered by false positive results and time consumption, which urged for newer biomarkers. Apelin is an adipokine that has gained a lot of attention due to its role in glucose metabolism and insulin sensitivity. This review aims to examine Aplin's diagnostic, predictive, and prognostic role among pregnant women with GDM. An online search took place throughout 4 electronic repositories (WOS, Scopus, Google Scholar, and PubMed) for keywords (GDM, insulin resistance, insulin sensitivity, screening, prognosis, fetal complication, and maternal complication). Extracted articles were screened for duplication, and data of interest were analyzed. Analysis confirmed a significant association of Aplein with GDM. Apelin levels were elevated or disturbed in cases that suffered from hyperglycemia, insulin resistance, or complications. It is important to mention that the evidence was sometimes inconsistent or contradictory; still, the results were promising. Apelin was a promising marker in GDM prediction, prognosis, and treatment. Many of the studies were hindered by heterogeneity, inconsistent diagnostic criteria, and small sampling. Future work is recommended to gain a deeper insight into Aplin's action and translate it into clinical practice for improving feto-maternal outcomes.

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INTRODUCTION

GDM is a state of glucose intolerance that affects pregnant during 24-28 weeks of gestation, leading to a state of hyperglycemia. It is a prominent health problem with a global incidence of around 9%. Although the underlying cause of GDM is not well understood, women with GDM suffer from failure of the body to secret higher insulin to meet the elevated requirement during pregnancy, leading to insulin resistance (IR) [1,2].

Pregnant deemed to have GDM usually have risk factors, including positive family history, previous personal history of GDM, advanced maternal age, and obesity [3].

Gestational diabetes imposes significant implications on the fetomaternal complications. On the material side, there is a higher risk of birth trauma and instrumental delivery risk of C-sections; additionally, they are prone to superimposed hypertension. In the long run, 50% of them have type-2 diabetes within 5 years after the delivery, and some have increased cardiovascular risk [4].

On the fetal side, they have a higher incidence of macrosomia with associated increases in interventions and operative delivery, higher risk of RDS, and neonatal complications. The complication may expand beyond neonatal to childhood with metabolic problems such as childhood obesity [5].

Screening methods for GDM include assessing patients' history for risk factors mentioned earlier, which is limited by some missed cases. The second method is lab screening, which includes;

1. An oral glucose tolerance test (OGGT) is where the patient fasts overnight and 75 or 100 mg of glucose is given, followed by one step or two steps (1- or 2 hours) post-prandial glucose testing. This test is hindered by being time-consuming, distressing to the patient, and shows variability as it is affected by stress and test timing [2,6]
2. Glucose challenge test (GCT): here, over one night fast, the patient drinks 50 grams of sugar and assesses blood glucose after 1 hour. False positive results and limited specificity limit the test [3,6].

HbA1C has also been used to evaluate blood glucose levels in the past 2 months, which serves as a prognostic and follow-up rather than screening.

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The most common method used for GDM screening is OGTT and GCT. Still, there are variations in testing protocol and test choice between 1- or 2-hour post-prandial screening and the population to be tested, i.e., universal screening versus high-risk population screening [4-6]. From the pathophysiological point of view, GDM does not include only disturbed glucose metabolism but also insulin resistance (IR), inflammations, and placental dysfunction. For that, the current method of GDM screening does not meet and cover all these abnormalities 6].For that, there was an urgent need for newer biomarkers that capture and meet these needs, offering a more comprehensive assessment of GDM risks, progression, and follow-up. In addition, we need more personalized biomarkers that are both noninvasive and accurate diagnoses based on individualized patients' needs. This allows improved fetal-maternal outcomes via timed intervention that reduces complications [7]. Apelin is a naturally occurring peptide known as a ligand for G-protein-coupled receptors. Its receptors are distributed in various tissues, such as the brain, blood vessels, the placenta, and the neonate[8].

Adipose tissues produce Apelins, and they have been shown to regulate glucose metabolism and insulin sensitivity [9]. It has been extensively examined, and research confirmed it has multiple roles as an immunomodulator, energy metabolism regulator, and anti-inflammation action [10].

Newer studies have suggested that it will have an essential role in metabolism-related obesity, such as type II DM, GDM, CVS, and hyperlipidemia. Pregnancy is known as a hyperdynamic state that is associated with metabolic changes in the mother's body, including hyperlipidemia-reduced IS, which suggests a key role of Apelin in these metabolic changes [11]. Apelin levels are altered during pregnancy owing to changes in the patient's nutritional status, IR, and obesity; all these parameters are closely linked to GDM. The exact role of adipokines in GDM pathophysiology is not fully understood; this review aims to examine apelin's role in GDM and define its potential application in GDM prediction, diagnosis, and prognosis [12].

Searching strategies

An online search took place throughout four electronic repositories (WOS, Scopus, Google Scholar, and PubMed) for keywords (GDM, insulin resistance, insulin sensitivity, screening, prognosis, fetal complication, and maternal complication). Extracted articles were screened for duplication, and data of interest were analyzed.

Predictive and Diagnostic role of apelin in GDM

Currently, the supporting data for Apelin in diagnosis is inconsistent, although many studies have confirmed its role in prediction, especially among high-risk pregnancies, which enables timely intervention. However, these studies investigating predictive roles were hindered by their small size and cross-sectional design; larger and longitudinal studies are needed. In everyday practice, the traditional OGTT is used to diagnose GDM. Some of the reported studies on Aplein's role in diagnosis and prediction are listed in Table 1.

As it is clear from the table, there was a discrepancy and inconsistency in the results that were reached. Sun et al. meta-analysis attributed these inconsistencies to commercial ELIZA kits, which affect the test results and thus the study outcome and recommendations [13].

De Gennaro's- analysis suggested that inconsistency in the diagnostic test used for GDM screening and failure to address confounders were the reasons for the failure to reach conclusive results with respect to apelin in GDM and advised standardization of test used [14].

Table 1. Studies that address Apelin role in GDM diagnosis and predction

Authors name	Study finding	Suggested action
Yan Guo [15]	Apelin levels were high in pregnant with GDM during 2nd trimester, and no difference was detected in 3rd trimester.	Support apelin role in physiological changes during pregnancy.
Kiyak et al. [16]	Aplin was significantly higher among fasting pregnant moms	Apelin levels are correlated with insulin resistance during fasting
Aslan et al. [17]	Apelin was higher among pregnant women with GDM; however, it was not correlated to insulin levels or HOMA-IR, and it failed to show significant changes in cord blood.	Apelin was not recommended as a reliable marker in GDM.
Castan-Laurell [18]	Apelin levels were reduced after 1st trimester in obese pregnancies following diet.	Apelin levels were correlated to IR.
Soriguer *et al* [19]	Apelin levels were strongly correlated to blood glucose and triglyceride in severely obese women, and Apelin levels were lowered among GDM cases.	Apelin levels were unrelated to obesity.
O'Harte *et al* [20]	Aplin was strongly related to lipids in GDM cases.	Apelin has a role in glucose and lipid metabolism.
Salman et al. [21]	Apelin levels were higher among cases with GDM and were strongly correlated to markers for GDM screening.	Apelin was recommended as a reliable marker in GDM screening.

Prognostic role for adverse feto-Maternal outcome

Pregnancy ay with GDM is regarded as a high-risk pregnancy, so close monitoring is needed to capture them earlier, which enables an intervention approach and therapeutic strategy for better feto-maternal outcomes. See Figure 1.

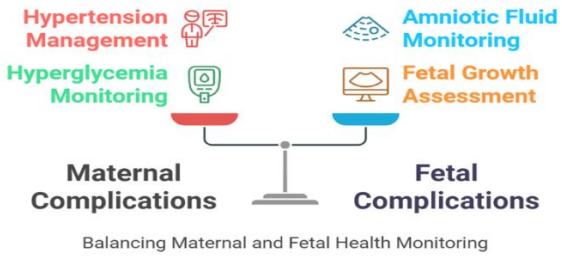

Figure 1. Fetomaternal monitering in GDM

Apelin was used as a prognostic marker among cases with GDM; many studies recommended it as a reliable marker; see table 2. Women who have disturbed levels can get

benefits from close monitoring during pregnancy. Additionally, they may be followed up postpartum for long periods to reduce Type-2 DM risk.

Table 2. Studies that address Apelin's role in predicting GDM-related complications

Authors	Study highlights	Apelin's Role in Complications
Nikolaos Loukas et al. [22]	Apelin was linked to fetal growth abnormality via the regulation of glucose metabolism and inflammation.	Apelin was recommended as a prognostic marker among DM and other complications.
Senjuti Dasgupta et al. [23]	Lowers levels of Apelin were found among cases that suffered from preterm labor and lower birth weight	the study confirmed apelin role as a prognostic marker for complication in the mother and her neonate
Nathalie Braun et al. [24]	Lowers levels of Apelin were found among cases who suffered adverse preanal outcomes	It was recommended as prognostic markers that practice complications.
Zuhal Karaca Karagoz et al. [25].	Higher levels of Apelin -13 and 36 were linked with higher glucose and triglyceride levels.	Apelin was linked to adverse maternal outcomes; its role in the neonate is unconfirmed yet.
Sun et al[13]. .	This systemic review found no differences between apelin levels in diabetic vs. healthy controls.	Since no link was found, it was not recommended as a marker.
Cevat Rıfat Cündübey et al.[16]	Apelin was not associated with complications among diabetic moms with	Since no link was found, it was not recommended as a marker

Therapeutic Role of Apelin in GDM Cases

The close relationship between apelin and energy mentalism during exercise, in which elevated levels were noticed, had encouraged using exercise and physical activity among pregnant as a non-pharmacological intervention to reduce the risk of severe hyperglycemia [27]. Animal studies have shown a promising therapeutic role for apelin. Giving it to rodents with diabetes caused improvement in glucose and lipid metabolism and reduction of oxidative stress. Stimulating glucose uptake by the muscles via the AMP-activated protein kinase (AMPK) pathway improved IS [28]. Apelin-13 was examined for that application owing to its stability and biological activity [29].

It seems that the evidence behind modulating the cholinergic system (APJ)is promising among GDM cases by improving sensitivity and glucose metabolism. Future research is needed to verify the safety, efficacy, and optimal delivery methods among pregnant moms, which enables translating its benefits into clinical practice [30].

Areas of future studies

Future works should dive into understanding the exact mechanism behind APJ system action and the way it modulates placental and fetal development [31]. Gene therapies are another promising therapeutic avenue that, when modulated, may allow for rectifying abnormal pregnancies. Investigating apelin gene polymorphisms and their link with GDM may explain the onset and severity across diverse populations [32]. Longitudinal studies are recommended to assess the risk of metabolic diseases and cardiovascular risk in postpartum women who suffer from GDM [33].

CONCLUSION

The role of apelin in GDM is promising; it seems to be closely linked to gestational diabetes pathophysiology and is involved in its progression and complications. Despite the inconsistency, apelin deserves further studies to validate and explore more applications in clinical practice.

Conflict of interest. Nil

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