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Case Control Study

Osteoprotegerin, interleukin and hepatocyte growth factor for prediction of diabetes and hypertension in the third trimester of pregnancy

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Abstract

BACKGROUND

Gestational diabetes mellitus (GDM) raises the risk of high blood pressure and may cause a series of life-threatening complications in pregnant women. Screening and management of GDM and gestational hypertension (GH) in pregnancy helps to control and reduce these risks and prevent adverse effects on mothers and their fetuses. Currently, the majority criteria used for screening of diabetes mellitus is oral glucose tolerance tests, and blood pressure test is usually used for the screening and diagnosis of hypertension. However, these criteria might not anticipate or detect all GDM or GH cases. Therefore, new specific predictive and diagnostic tools should be evaluated for this population. This study selected three biomarkers of osteoprotegerin (OPG), interleukin (IL) and hepatocyte growth factor (HGF) for GDM and GH predication and diagnosis.

AIM

To explore the feasibility of changes in placental and serum OPG, IL and HGF as tools for prediction and diagnosis of diabetes and hypertension in pregnant women.

METHODS

From January 2018 to January 2019, 44 pregnant women with GDM and GH were selected as an observation group, and 44 healthy pregnant women were selected as a control group in the same period. Serum OPG, IL and HGF were compared between the two groups.

RESULTS

The levels of OPG and HGF in the observation group were lower than in the control group, and the level of IL-1 β was higher in the observation group than in

conflicts of interest.

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the control group (all $P < 0.05$). Furthermore, OPG and HGF were negatively associated with gestational diabetes and gestational hypertension, while IL-1 β was positively associated with GDM complicated with GH (all $P < 0.05$).

CONCLUSION

The evaluation of serum OPG, HGF and IL-1 β levels in patients with coexistent gestational diabetes complicated with hypertension can predict the degree of disease and play an important role in the follow-up treatment and prognosis prediction.

Key Words: Third trimester of pregnancy; Osteoprotegerin; Interleukin; Hepatocyte growth factor; Gestational diabetes mellitus; Gestational hypertension

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Core Tip: Gestational diabetes mellitus (GDM) and gestational hypertension (GH) are associated with serious and long-term fetomaternal and neonatal outcomes compared to normal pregnancies. Although oral glucose tolerance tests and blood pressure tests were accepted criteria for screenings of GDM and GH, these criteria might not anticipate or detect all GDM or GH cases. Biomarkers may serve as adjunct predictors for GDM and GH. The present study explored osteoprotegerin, interleukin and hepatocyte growth factor for prediction of GDM and GH.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a disease associated with impaired glucose tolerance and glucose intolerance during pregnancy^[1-2]. Studies^[3-6] showed that the incidence of GDM was 1% to 5%. The onset and development of GDM is usually caused by overnutrition, rapid weight gain and lack of exercise during the pregnancy. In the clinical practice, the incidence of GDM has increased in recent years. Moreover, 30% of women with GDM have a higher risk of gestational hypertension (GH), and the risk is three to five times than the pregnant women without GDM. These two diseases have a great impact on the prognosis of fetuses and the mothers. Pathogenic factors for GDM are complex. Some studies^[7-10] pointed out marker levels including osteoprotegerin (OPG), interleukin-1 β (IL-1 β) and hepatocyte growth factor (HGF) may be factors in predicting the severity of a disease. Early detection of changes in a patient's condition can help to reduce the incidence of hypertension and improve the outcomes of pregnancy. The present study explored the significance of detection of OPG, IL-1 β and HGF in the placenta and serum in evaluating and predicting the onset and development of gestational diabetes and hypertension in the third trimester of pregnancy.

MATERIALS AND METHODS

Participants

A total of 44 pregnant women with GDM and GH were selected as an observation group from January 2017 to December 2018. Another 44 healthy pregnant women were selected as a control group. Eligibility criteria^[11-13] for participants included: participants in the observation group were diagnosed with GDM and GH in accordance with diagnostic code; the present study was approved by the ethics committee of our hospital; patient adherence to therapy was high and therefore the

subsequent research was conducted successfully; and no other diseases occurred influencing the development of the study. Patients with immune disorders or mental illness and patients who used drugs that affect lipid metabolism recently were considered ineligible. The average age was 28 to 39 years (34.5 ± 1.8) in the observation group and 27 to 36 years (33.2 ± 1.9) in the control group. There was no significant difference in patient information between the two groups ($P > 0.05$).

Methods

Five milliliters of blood were drawn from each of the participants. The collected samples were centrifuged at 3500 r/min for 10 min. Then the supernatants were kept at -80°C for testing. Enzyme linked immunosorbent assay was used to test the levels of serum OPG and IL-1 β with reagents from Beijing Derman International Freight Forwarding Co., Ltd., which were produced by Biomedica, Wien, Österreich, Austria. HGF was tested using immunohistochemistry. All the procedures were performed strictly based on the kit instructions.

Measurements

Levels of OPG, IL-1 β and HGF were compared between the two groups.

Statistical analysis

SPSS18.0 and Student's *t* test were used to process data in the study. Quantitative data was expressed as mean \pm standard deviation, and dichotomous data was expressed as percentage. $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Levels of OPG, IL-1 β and HGF

Levels of OPG and HGF were lower in the observation group than in the control group ($P < 0.05$). However, levels of IL-1 β were higher in the observation group than in the control group ($P < 0.05$, Table 1).

Relationship between GDM and GH and OPG, IL-1 β and HGF

OPG and HGF were negatively associated with GDM and GH, and IL-1 β was positively associated with GDM and GH (all $P < 0.05$, Table 2).

DISCUSSION

The incidence of GDM is increasing worldwide in recent years. It may range from 1% to 14% in the world and 1% to 5% in China. The causes of GDM are complex. One of the common complications is macrosomia followed by abortion, shoulder dystocia, laceration of birth canal, *etc.* Moreover, GDM may lead directly to fetal overgrowth and puts offspring at high risk of diabetes during pregnancy^[14,15]. Several studies^[16-18] revealed that the incidence of GH increases in the above population. The incidence of eclampsia, serious eclampsia and pre-eclampsia is 3.9%, 4.5% and 4.4%, respectively. GH has a great effect on maternal and child health and is a common reason accounting for the increasing maternal and perinatal mortality. Accordingly, early diagnosis and treatment can help to improve the prognosis and reduce the incidence of complications.

OPG functioning as a soluble decoy receptor is a member of the tumor necrosis factor family. In pregnant women with GDM, changes in the levels of OPG may be associated with insulin levels and obesity. Cytokine-induced OPG can help to protect pancreatic β cells from being further injured. Additionally, Bogdanet *et al*^[19] confirmed that changes in the levels of OPG may have an impact on vascular endothelial function and the development of complications. Thereby, OPG is an important indicator in predicting cardiovascular events.

IL-1 β plays a significant role in the progression of pancreatic inflammation. Animal testing showed that apoptosis in pancreatic β cells occurred when they were exposed to IL-1 β . Furthermore, Anderlová *et al*^[20] reported that IL-1 β is an important factor influencing endothelial cell injury. It is the central tache for hypertension and also for GH.

HGF is an essential human cytokine that is mainly produced by placental tissues. HGF increases vasodilation in the microvascular circulation, resists pancreatic β

Table 1 The comparison of levels of osteoprotegerin, interleukin-1 β and hepatocyte growth factor between the two groups

Group	OPG, pmol/L	IL-1 β , ng/L	HGF
Observation group	1.94 \pm 0.09	145.65 \pm 9.45	5.65 \pm 1.65
Control group	2.24 \pm 0.14	45.65 \pm 6.45	11.65 \pm 2.56
<i>t</i>	11.957	57.976	13.069
<i>P</i> value	0.001	0.001	0.001

HGF: Hepatocyte growth factor; IL-1 β : Interleukin-1 β ; OPG: Osteoprotegerin.

Table 2 Correlation between gestational diabetes mellitus and gestational hypertension and osteoprotegerin, interleukin-1 β and hepatocyte growth factor

Indicators	GDM and gestational hypertension	
	<i>r</i>	<i>P</i> value
OPG	-0.556	< 0.05
IL-1 β	0.456	< 0.05
HGF	-0.659	< 0.05

GDM: Gestational diabetes mellitus; HGF: Hepatocyte growth factor; IL-1 β : Interleukin-1 β ; OPG: Osteoprotegerin.

proliferation and decreases blood glucose. It may play an important role in the prevention of GH in pregnant women with GDM.

The present study found that there was significant differences in the levels of OPG, HGF and IL-1 β between healthy pregnant women and pregnant women with GDM complicated with GH (all *P* < 0.05). OPG and HGF were negatively associated with and IL-1 β was positively associated with the incidence of GDM and GH in pregnant women. Studies showed that OPG, HGF and IL-1 β were important cytokines and inflammatory factors that are actively involved in the development of GDM and GH. Detection of the above indicators can provide an important basis for the treatment decision and prognosis prediction.

CONCLUSION

In general, detection of OPG, HGF and IL-1 β levels can help to predict severity of gestational diabetes and hypertension in pregnant women, which plays an important role in treatment selection and prognosis prediction.

ARTICLE HIGHLIGHTS

Research background

Gestational diabetes mellitus (GDM) and gestational hypertension (GH) exerts serious effects on the health of perinatal pregnant women and fetuses. Clinical screening of GDM and GH may attenuate the associated disorders in women and offspring. Currently, GDM diagnosis is based on evaluation of glucose tolerance tests at late stages of pregnancy but increased age, body weight and history of GDM may conditionate this criterion. For instance, it was found that using fasting plasma glucose criteria alone, more GDM diagnoses were missed in women \geq 35 years than in women < 35 years. A simple and effective way is needed to predict GDM and GH in this population.

Research motivation

Interleukin-1 β (IL-1 β) has been implicated as a key proinflammatory cytokine involved in the pancreatic islet inflammation of diabetes mellitus. Hepatocyte growth

factor (HGF) plays a central role in metabolic disorders and contributes to insulin resistance and diabetes pathophysiology. Osteoprotegerin (OPG) is a soluble glycoprotein and is involved in different metabolic alterations such as diabetes, obesity, hypertension and metabolic syndrome. Thus, levels of IL-1 β , HGF and OPG could be selected as biomarkers for disease status and progression of GDM and GH in pregnant women.

Research objectives

The aim of this study was to explore the efficacy of detection of placental and serum OPG, IL-1 β and HGF for prediction and diagnosis of diabetes and hypertension in pregnant women.

Research methods

In total, 44 pregnant women with GDM and GH were selected as an observation group, and 44 healthy pregnant women were selected as a control group in the same period. OPG, IL-1 β and HGF were compared between the two groups.

Research results

The levels of OPG and HGF in the observation group were lower than in the control group, and the level of IL-1 β was higher in the observation group than in the control group. Furthermore, OPG and HGF were negatively associated with GDM and GH, while IL-1 β was positively associated with GDM complicated with GH.

Research conclusions

The evaluation of serum OPG, HGF and IL-1 β levels in patients with coexistent gestational diabetes complicated with hypertension can predict the degree of disease and play an important role in the follow-up treatment and prognosis prediction.

Research perspectives

More clinical and validation studies should be conducted to further evaluate the performance of biomarkers of OPG, IL-1 β and HGF for GDM and GH predication and diagnosis including sensitivity, specificity and accuracy before potential use of these biomarkers as predictors in clinical practice.

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