Original Articles/นิพนธ์ต้นฉบับ

Can Adiponectin Predict Hypertensive Disorder in Pregnancy?

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Abstract

Objectives: To determine whether adiponectin can predict hypertensive disorder in pregnancy (HDP).

Methods: All women with singleton pregnancy and who were at risk of gestational diabetes mellitus (GDM) were studied. They underwent a 50 gram glucose challenge test (GCT) and a blood sample test for adiponectin between 21 and 27 weeks gestation. Subsequently, between 24 and 28 weeks gestation the women underwent a 100 gram oral glucose tolerance test (OGTT). The pregnancy and perinatal outcomes in all women were observed and analyzed.

Results: There were 359 women enrolled in this study. Twenty-two cases of HDP (6.1%) and 60 women with GDM (16.7%) were diagnosed. There were no significant difference in age, pre-pregnant BMI, sampling day BMI, weight gain on sampling day and total weight gain during pregnancy in both groups. Serum adiponectin was not significantly lower in HDP than non - HDP women (P = NS). There was a relationship between pre-pregnant BMI and total adiponectin levels in HDP (p=0.0143). The area under the receiver-operator characteristic curve was 0.5853. In order to predict HDP, an arbitrarily cut-off value of adiponectin was determined. With the adiponectin cut-off value < 4.4 μg/ml, the sensitivity, specificity, PPV and NPV were 4.55%, 90.50%, 4.76% and 93.14% respectively. At this cut-off value, only 1 out of 22 cases of HDP could be identified.

Conclusion: The levels of adiponectin in women with HDP were not significantly different from those without HDP and could not predict HDP.

Keywords: Adiponectin, hypertensive disorder in pregnancy, preeclampsia, insulin resistance, hypertension, pregnancy

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Introduction

Hypertensive disorders in pregnancy (HDP) is still a major cause of maternal morbidity and mortality and is one of the three major causes of maternal death together with hemorrhage and infection.[1] HDP, according to the National High Blood Pressure Education Program[2] includes several disorders: gestational hypertension (GH), preeclampsia, eclampsia and chronic hypertension with or without superimposed preeclampsia. The pathogenesis and etiology of hypertensive disorders in pregnancy remains unclear.

Recently, a number of authors have reported an association between insulin resistance and HDP.[3-5] The development of insulin resistance in the 3rd trimester of pregnancy together with adipose tissue accumulation are possible adaptations of the maternal metabolism to optimize sufficient energy and fetal nutrition.[6,7] In addition, the placenta secretes a variety of hormones that may play roles in both gestational insulin resistance and HDP. Pathologically, extensive insulin resistance is often observed during HDP.[8]

Adiponectin, which is exclusively produced by fat tissue, is a collagen-like hormone, and has the properties of being antidiabetic and antiatherogenic, with enhancement of insulin sensitivity.[9,10] This hormone is inversely associated with insulin resistance and obesity.[11]

Marzaki-Tovi et al.[12] observed that adiponectin levels did not differ between the 1st, 2nd and 3rd trimesters of pregnancy. However, these levels were significantly higher than that of the postpartum period. Conversely, Fuglsang et al.[13] reported that serum adiponectin peaked in mid-pregnancy. There have been reports of adiponectin in HDP with controversial results. An elevation of adiponectin was observed by some authors[14,15] but a decline of this hormone was observed by the others.[16-18]

The objective of this study was to determine whether adiponectin could predict HDP.

Materials & Methods

This study was conducted between 2004-2005 in the Department of Obstetrics & Gynecology, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. The study was approved by the Ethical Clearance Committee on Human Right Related to Researches Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Thailand. Informed consent was obtained from each patient.

Samples

The women included in this study were singleton pregnancy, previously healthy with uncomplicated pregnancies and who were at risk of gestational diabetes mellitus (GDM). The indication for GDM screening, using recommendations of the American College of Obstetricians and Gynecologists (ACOG) for GDM screening[19] were as follows: (1) maternal age > 30 years; (2) obesity; (3) family history of diabetes mellitus (DM); (4) prior GDM; (5) glucosuria; (6) a patient has symptoms or signs suggestive of hyperglycemia; and (7) a history of poor obstetric outcome.

All pregnant women received a routine ultrasound scan to confirm gestational age and the number of fetuses at 18-20 weeks of gestation. The eligible pregnant women had their medical and obstetric history obtained by interview and underwent a physical examination.

Woman with hypertension, a known diagnosis of DM and chronic disease that required treatment were excluded from the study.

Hypertension during pregnancy was defined as blood pressure ≥140/90 mm Hg. Proteinuria refers to 24 hour urine protein ≥300 mg or ≥1 g/l (1+ dipstick).

Gestational hypertension (GH) was defined as

hypertension developing after 20 weeks of gestation in a previously normotensive women which returned to normal <12 weeks' postpartum. Preeclampsia was hypertension plus proteinuria. Chronic hypertension was hypertension before pregnancy or before 20 weeks of gestation[2].

Intervention

The two-step approach technique for the evaluation of GDM according to ADA recommendations was performed in all women. A 1-h 50-g GCT was performed between the 21st and 27th week of gestation. Subsequently, a 3-h 100-g OGTT was done between the 24th and 28th week of gestation.[19]

On the same day before performing the 50-g GCT, body weight and height were measured and blood samples for adiponectin concentrations were also obtained.

All blood samples for glucose determination were immediately centrifuged at room temperature. Plasma was separated and determinations performed within 1 h. The blood samples for adiponectin determination were also immediately centrifuged at 430 G/min for 15 min at 4°C. Plasma was stored at -70°C until assayed.

Laboratory assays

Glucose concentrations were determined using the hexokinase-glucose-6-phosphate dehydrogenase method with an automatic chemistry analyzer (Dimension; Dade Behring Inc., Newark, NJ, USA).

Adiponectin concentrations were measured using a standardized immunoassay kit (Linco Research, Inc., St. Charles, MO, USA). ^{125}I- labeled adiponectin and anti- adiponectin rabbit antiserum were used to determine adiponectin concentrations with the double antibody / polyethylene glycol technique. The intra- and inter-assay coefficients of variation at the adiponectin concentration range of 3-15 μg / ml were 1.8-6.2 % and 6.9-9.3 %, respectively.

The ADA criteria for the diagnosis of GDM were used. (20) The diagnosis of GDM was established when two or more of the following criteria were fulfilled: (1) fasting glucose > 95 mg/dl; (2) 1-h glucose > 180 mg/dl; (3) 2-h glucose > 155 mg/dl; (4) 3-h glucose > 140 mg/dl

Statistical analysis

Body mass index (BMI) was calculated as body weight (kg) / height (m^2). Data were presented as mean ± standard deviation and frequency (%). If the data were not normally distributed, the median (5^{th}–95^{th} percentile) was also presented. All analyses were performed using STATA version 9.0 (Stata Corp., College Station, TX, USA) and logistic regression. A *p* value < 0.05 was considered statistically significant.

Results

There were 359 pregnant women enrolled in this study. Twenty-two cases of HDP (6.1%) and 60 cases of GDM (16.7%) were observed in this study.

There were no significant differences in age, pre-pregnancy BMI, sampling day BMI, weight gain on sampling day and total weight gain during pregnancy (Table I). Blood pressure at 28 weeks' gestation in non HDP women and those at the time of diagnosis in case of HDP were compared. Both systolic and diastolic blood pressures were significantly higher in HDP than non-HDP (p 0.001) women. Adiponectin levels measured at 21-27 weeks were not significantly different between HDP and non- HDP subjects. The gestational age at delivery (p< 0.001) and birth weight (p< 0.001) were significantly lower in HDP than non- HDP subjects. Table II demonstrates the correlation between adiponectin levels and blood pressure, pre-pregnancy BMI, sampling day BMI and weight gain on sampling day. There was no correlation between adiponectin levels and either systolic or diastolic blood pressure in pregnant women. In contrast, there was a negative relationship between

Table I Characteristics and adiponectin levels in pregnant women with and without HDP

	Total (n=359)	HDP (n=22)	Non- HDP (n= 337)	P*
Age (years)	31.8±6.1	32.8±5.1	31.8±6.2	0.4271
Pre-pregnancy BMI (kg/m^2)	23.2±4.3	24.0±4.7	23.2±4.3	0.3990
Sampling-day BMI (kg/m2)	25.6±4.6	26.2±4.8	25.6±4.6	0.5280
Weight increase sampling-day (kg)	5.9±4.7	3.5(1-19)	5(2-27)	0.4812
Total weight gain (kg)	13.0±4.2	12.1±3.8	13.0±4.2	0.3009
Systolic blood pressure (mmHg)	110.2±16.3	151.6±6.4	101.5±12.8	0.0000
Diastolic blood pressure (mmHg)	74.3±11.5	100.7±3.6	72.6±9.6	0.0000
GDM (n / percent)	60 (16.7)	4 (18.2)	56 (16.6)	0.8491
Adiponectin (ฑg/ml)	7.3	5.3	7.3	0.1798
	(1.3-51.5)	(1.7- 51.5)	(1.3-50.2)	
GA at delivery (weeks)	38.1±1.6	37.0±3.0	38.2±1.4	0.0002
Birth weight (gram)	3051.0±498.5	2660.0±506.8	3083.5±481.3	0.0001

Data are shown as Mean ± SD, Median (5th-95th percentile) and number (%)

GDM : gestational diabetes mellitus ; GA : gestational age

* compared between HDP and non-HDP

Table II Correlation between adiponectin ,BMI and blood pressure

	Adiponectin level					
	Total (n=359)		HDP (n=22)		Non-HDP (n=337)	
	r	p	r	p	r	p
Blood pressure						
Systolic	-0.0058	0.9124	-0.1728	0.4419	-0.0056	0.9185
Diastolic	-0.0382	0.4713	-0.1596	0.4781	-0.0525	0.3376
Pre-pregnancy BMI	-0.0140	0.7922	-0.5146	0.0143*	-0.0905	0.0970
Sampling-day BMI	-0.0688	0.1933	-0.4189	0.0523	-0.1372	0.0117*
Weight gain on sampling- day	-0.1274	0.0157*	-0.2103	0.3474	-0.1188	0.0292*

r : Pearson correlation coefficient

*p = significant

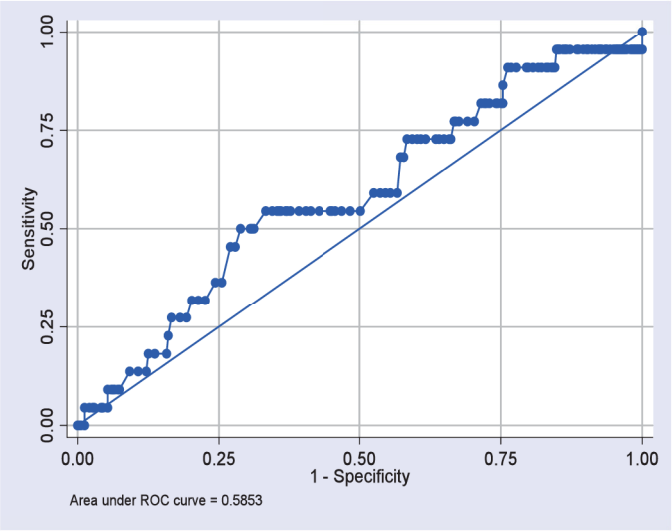

Fig.1 *ROC curves between serum adiponectin levels and HDP*

weight gain on sampling day and total adiponectin levels in all pregnant women (p 0.0157) and non-HDP (p 0.0292). While pre-pregnancy BMI was a negative correlation with adiponectin in HDP (P 0.0143). Sampling-day BMI was shown a negative correlation with adiponectin level in non-HDP (p 0.0117)

The area under the ROC (receiver-operator characteristic) curve was 0.5853 (Fig.1). In order to predict HDP, we arbitrarily determined a cut-off value of adiponectin with high specificity and negative predictive value for the diagnosis of HDP. At the cut-off value < 4.4 μg/ml, the sensitivity, specificity, positive predictive value and negative predictive value were 4.55%, 90.50%, 4.76% and 93.14% respectively.

Discussion

HDP is a serious and frequent complication in pregnancy and its pathogenesis is incompletely understood. The prevalence of HDP in this study was 6.1% which is similar to other reports.[21] Previous studies have shown that insulin resistance (IR) appears to be associated with HDP.[4,5] Physiologically, IR and resultant hyperinsulinemia are common in normal pregnancy and are maximal in the third trimester. These conditions rapidly return to pre-pregnancy levels after delivery[21]. In fact, IR and hyperinsulinemia are more severe in women with HDP than those without.[4,21]

HDP is more prevalent in pregnant women with IR.[21], obesity[21,22] and in those with GDM[1]. In view of the known associations between adiponectin and these conditions, these formed the focus of the current study. Adiponectin is an adipocyte-specific, collagen like hormone which correlates inversely with IR and obesity.[9,11,23,24] It is also thought to have an effect on vascular endothelial function[25], a major factor in the pathophysiology of HDP. The association between plasma adiponectin levels and HDP remains controversial. Some authors have demonstrated increased adiponectin levels in women with HDP[14,15] whilst others have shown a decrease[16,18,21] or no change[26]. The current study confirms the result of O' Sullivan et al[26] with no difference in total adiponectin levels in women with and without HDP. With the arbitrary adiponectin cut-off value of < 4.4 μg/ml, the specificity and NPV for diagnosing HDP were high (90.50% and 93.14%, respectively). However, with this cut-off value, we could only identify HDP in 1 out of 22 cases.

In this study, total adiponectin was not a reliable predictor for HDP. There are a number of possible explanations for these disparate findings. Importantly,

there are three forms of adiponectin in circulation, namely low, middle and high molecular weight (HMW) species.[27] Previous studies have shown that HMW adiponectin is more closely associated with 2-hour post load glucose levels than total adiponectin levels[28]. HMW adiponectin is also a better predictor of glucose intolerance than total adiponectin.[28] Catalano, et al[29] previously reported that HMW adiponectin correlated well with IR in pregnant women. In the current study, only total adiponectin levels were measured and were not predictive of HDP.

Ethnicity[30] and obesity have also been shown to influence adiponectin levels in some[22,31,32] but not all[26] studies. In the current study, the women were ethnically homogenous and there was a negative relationship between BMI and total adiponectin levels particularly pre-pregnant BMI and HDP.

In conclusion, the levels of total adiponectin at 21-27 weeks do not predict HDP. Further research with a larger population and using the HMW of adiponectin would be of interest.

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Original Articles/นิพนธ์ต้นฉบับ

ระดับสาร Adiponectin สามารถใช้ทำนายการเกิดภาวะความดันโลหิตสูงในสตรีตั้งครรภ์ได้หรือไม่

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาความเป็นไปได้ที่จะใช้ระดับสาร Adiponectin ในการทำนายการเกิดภาวะความดันโลหิตสูงในสตรีตั้งครรภ์

วิธีการ: ศึกษาในสตรีตั้งครรภ์เดี่ยวที่มีเกณฑ์เสี่ยงต่อการเกิดภาวะเบาหวานในขณะตั้งครรภ์ โดยทุกรายจะได้รับการตรวจเลือดหาค่า 50gm glucose challenge test และค่า Adiponectin ที่ระหว่างอายุครรภ์ 21-27 สัปดาห์ หลังจากนั้นจะได้รับการตรวจหาค่า 100 gm oral glucose tolerance test ที่ระหว่างอายุครรภ์ 24-28 สัปดาห์ แล้วเก็บข้อมูลศึกษาผลของการตั้งครรภ์ทั้งต่อมารดาและทารกในครรภ์

ผลการศึกษา: จากการศึกษาสตรีตั้งครรภ์เดี่ยว 359 รายที่มีเกณฑ์เสี่ยงต่อการเกิดภาวะเบาหวานในขณะตั้งครรภ์ พบว่ามีอุบัติการเกิดภาวะความดันโลหิตสูงในสตรีตั้งครรภ์ 22 ราย (ร้อยละ 6.1) ภาวะเบาหวานในขณะตั้งครรภ์ 60 ราย (ร้อยละ 16.7) ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติในกลุ่มที่มีและไม่มีภาวะความดันโลหิตสูงในสตรีตั้งครรภ์ในด้านอายุ ค่าดัชนีมวลกาย (BMI) ก่อนการตั้งครรภ์ ค่าดัชนีมวลกาย (BMI) ในวันที่เจาะเลือด น้ำหนักที่เพิ่มขึ้นทั้งหมดระหว่างตั้งครรภ์ และระดับสาร Adiponectin แต่พบว่ามีความสัมพันธ์ระหว่างค่าดัชนีมวลกาย (BMI) ก่อนการตั้งครรภ์กับระดับสาร Adiponectin ในกลุ่มที่มีภาวะความดันโลหิตสูงในสตรีตั้งครรภ์ (p 0.0143) จากการศึกษา Receiver-operator characteristic curve พบว่าพื้นที่ใต้กราฟมีค่า 0.5853 ผู้วิจัยได้เลือกค่า Adiponectin น้อยกว่า 4.4 ไมโครกรัมต่อมิลลิลิตร เพื่อทำนายภาวะภาวะความดันโลหิตสูงในสตรีตั้งครรภ์ พบว่ามีค่า sensitivity, specificity, positive predictive value และnegative predictive value เท่ากับร้อยละ 4.55, 90.50, 4.76 และ 93.14 ตามลำดับ

สรุป: ระดับสาร Adiponectin ในสตรีตั้งครรภ์ที่มีภาวะความดันโลหิตสูง ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติกับกลุ่มสตรีตั้งครรภ์ที่ไม่มีภาวะความดันโลหิตสูง และไม่สามารถใช้ทำนายการเกิดภาวะความดันโลหิตสูงในสตรีตั้งครรภ์ได้