UNIVERSITI PUTRA MALAYSIA

IDENTIFICATION OF POTENTIAL PLASMA PROTEIN MARKERS FOR GESTATIONAL DIABETES MELLITUS

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IDENTIFICATION OF POTENTIAL PROTEIN MARKERS FOR GESTATIONAL DIABETES MELLITUS

By

PUSHPA GANDI SANGARAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

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This thesis is dedicated to my spiritual master Bhoghar for his unwavering support, understanding, strength, love, constant encouragement and for inspiring me with a belief in my own abilities.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

IDENTIFICATION OF POTENTIAL PROTEIN MARKERS FOR GESTATIONAL DIABETES MELLITUS

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September 2012

Chairman: **Professor Rozita Rosli, PhD**

Faculty : **Medicine and Health Sciences**

Gestational Diabetes Mellitus (GDM) is defined as glucose intolerance that is detected during pregnancy. It is caused by the decreased sensitivity of insulin with increasing gestation week. Identifying this group of women is important in not only preventing perinatal morbidity but also improving long term outcomes for the mothers and their children. The usual approach in diagnosing GDM is to screen GDM patients during the second trimester of gestation through an oral glucose tolerance test (OGTT). There is potential harm and high costs may be involved in screening, especially given the high false-positive rate. However, there is a need to diagnose GDM as early as possible to minimize the undesirable effects in the development of the fetus.

In this exploratory study, two dimensional gel electrophoresis (2DGE) and Liquid Chromatography Mass Spectrometry (LC/MS/MS) were used in the quest for new potential biomarkers for the disease. The purpose of this study was to identify a set of potential protein markers which are differentially expressed during the first, second or third trimester of pregnancy. Once identified and validated, the candidate biomarkers for GDM could provide

opportunities for rapid and low-cost screening. For this study, five millilitres of fresh blood was drawn for each trimester of pregnancy from five normal pregnant women and five GDM patients at Hospital Kuala Lumpur and Klinik Kesihatan Seri Kembangan. The plasma samples were used for 2DGE, where proteins are separated first by characteristic isoelectric point using isoelectrofocusing, and then by protein molecular weight, using sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The 2D gels were stained using Colloidal Coomassie Blue stain and scanned by using a high resolution imager. The images were quantitatively analyzed using Nonlinear Progenesis SameSpots Software to identify protein spots that demonstrate significant differences in expression between the GDM samples and with normal pregnant samples. Spots demonstrating significant differences were manually picked using sterile procedure and identified by LC/MS/MS analysis through a service from the Proteomics Centre at Medical University of South Carolina.

In this study, 11 distinct proteins were identified which were expressed differentially in the plasma of normal pregnant women and plasma from GDM patients. The proteins were Alpha-1-Antitrypsin, Albumin, Antithrombin III, Fibrinogen, Apolipoprotein A1, Apolipoprotein E, Alpha 1B-Glycoprotein, Complement Factors, Angiotensinogen, Transferrin, and Vitamin D binding protein. Among these proteins, Antithrombin III, Apolipoprotein E and Vitamin D binding protein could be candidates to screen the GDM patients. Further studies are recommended to validate these candidate biomarkers by using ELISA and western blotting.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Sarjana Sains

PENGENALPASTIAN PENANDA PROTEIN BERPOTENSI BAGI DIABETES MELLITUS SEMASA KEHAMILAN

Oleh

PUSHPA GANDI SANGARAN

September 2012

Pengerusi: Profesor Rozita Rosli, PhD

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Diabetes mellitus semasa kehamilan (GDM) ialah ketaktoleranan glukosa yang dikesan semasa kehamilan. Ini disebabkan oleh kemerosotan kesensitifan insulin yang berlaku sepanjang tempoh kehamilan. Kepentingan mengenal pasti kumpulan wanita yang terbabit dengan keadaan ini adalah penting bukan sahaja bagi menghindari mereka daripada kematian semasa kelahiran malahan juga bagi memperbaik kesan jangka panjang terhadap para ibu dan anak mereka. Pendekatan bagi mendiagnosis GDM biasanya ialah dengan menyaring penghidap GDM semasa trimester kedua kehamilan melalui ujian ketoleranan glukosa secara oral (OGTT). Penyaringan mungkin menyebabkan kesan yang buruk dan kos yang tinggi, terutamanya kerana kaedah ini melibatkan kadar positif palsu yang tinggi. Walau bagaimanapun, GDM perlu didiagnosis seawal yang mungkin bagi meminimumkan kesan kurang baik dalam perkembangan fetus.

Dalam kajian tinjauan ini, elektroforesis gel dua dimensi (2DGE) dan spektometri massa kromatografi cecair (LC/MS/MS) telah digunakan bagi menentukan beberapa penanda bio

berpotensi penyakit ini. Tujuan kajian ini adalah bagi mengenal pasti satu set penanda protein berpotensi yang diekspresi secara berbeza-beza semasa trimester pertama, kedua dan ketiga kehamilan. Calon penanda bio GDM yang telah dikenal pasti dan disahkan boleh digunakan dalam penyaringan yang pantas dan berkos rendah. Bagi kajian ini, lima milliliter darah diambil daripada lima wanita hamil yang normal dan lima penghidap GDM bagi setiap trimester kehamilan di Kuala Lumpur dan Klinik Kesihatan Seri Kembangan. Sampel plasma digunakan bagi 2DGE, di mana protein diasingkan melalui ciri-ciri titik isoelektrik menggunakan pemfokusan isoelektrik, dan kemudian secara berat molekular protein menggunakan elektroforesis gel dodesilsulfat poliakrilamida (SDS-PAGE). Gel 2D tersebut telah diwarnakan dengan pewarna biru Coomassie berkoloid dan diimbas dengan menggunakan pengimbas beresolusi tinggi. Imej dianalisis secara kuantitatif menggunakan perisian Nonlinear Progenesis SameSpots bagi mengenal pasti bintik protein yang menunjukkan perbezaan signifikan ekspresi antara sampel GDM dengan sampel kehamilan normal. Bintik yang menunjukkan perbezaan signifikan dipilih dengan tangan secara steril dan dikenal pasti melalui analisis LC/MS/MS oleh perkhidmatan Proteomics Centre di Medical University of South Carolina.

Sebelas protein berlainan telah dikenal pasti di mana semuanya terekspresi secara berbeza-beza di dalam plasma wanita hamil yang normal dan plasma wanita dengan GDM. Protein-protein itu ialah Alpha-1-Antitrypsin, Albumin, Antithrombin III, Fibrinogen, Apolipoprotein A1, Apolipoprotein E, Alpha 1B-Glycoprotein, Faktor Pelengkap, Angiotensinogen, Transferrin, dan protein penambat Vitamin D. Antara protein itu, Antithrombin III, Apolipoprotein E dan protein penambat Vitamin D berpotensi menjadi calon bagi menyaring penghidap GDM. Kajian lanjutan disyorkan bagi mengesahkan calon penanda bio dengan menggunakan ELISA dan mendapan Western.

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I certify that an Examination Committee has met on----------to conduct the final examination of Pushpa Gandi Sangaran on her Master of Science thesis entitled 'Identification of potential protein markers for Gestational Diabetes Mellitus' in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Pertanian Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the degree of Master of Science.

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DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously and is not concurrently submitted for any other degree at Universiti Putra Malaysia or at any other institutions.

PUSHPA GANDI SANGARAN

Date : 27 September 2012

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LIST OF ABBREVIATIONS

1,25(OH)-D	Calcitriol
2D-DIGE	2-Dimensional-Fluorescence Difference Gel Electrophoresis
2D-PAGE	2-Dimensional-Polyacrlamide Gel Electrophoresis
^{32}P	Phosphorus
3T3-L1	Mouse embryonic fibroblast-adipose like cell line) Nuclear Lysate
A1BG	Alpha 1B-Glycoprotein
AAT	Alpha-1-Antitrypsin
ALB	Albumin
ACOG	American College of Obstetricians and Gynaecologists
ADA	American Diabetes Association
Apo A1	Apolipoprotein A1
Apo E	Apolipoprotein E
AT3	Antithrombin III
BLAST	Basic Local Alignment Search Tool
BMI	Body Mass Index
BSA	Bovine Serum Albumin
CCB	Coomassie Brilliant Blue

CHAPS	3-[(3cholamidopropyl) dimethylammonio]-1-propanesulfonate
Cm	centimetre
DTT	Dithiothreitol
ELISA	Enzyme Linked Immunosorbent Assay
ESI-MS	Electrospray Ionization Mass Spectrometry
G	gravity
G	Gram
GCK	Glucokinase
GDM	Gestational Diabetes Mellitus
HCl	Hydrochloric acid
hCS	human Chorionic Sommatomammotropin
HDL	High Density Lipoprotein
HNF4a	Hepatocyte Nuclear Factor-4a
hPL	human Placental Lactogen
IDL	Intermediate Density Lipoprotein
IEF	Isoelectric Focusing
IGF2	Insulin-Like Growth Factor-2
INSR	Insulin Receptor
INS-VNTR	Insulin gene
IPG	Immobilised pH Gradient

IRS	Insulin Receptor Substrate
kDa	kiloDalton
Kg	kilogram
L	Litre
LC	Liquid Chromatography
LC/MS/MS	Liquid Chromatography Mass Spectrometry
LDL	Low Density Lipoproteins
LPL	Lipoprotein Lipase
M	Molar
MAC	Membrane Attacks Complex
MALDI-TOF	Matrix Assisted Laser Desorption Time Of Flight
MAP	mean arterial pressure
MS	Mass Spectrometry
mg/dl	milligram per decilitre
Ml	millilitre
mM	miliMolar
MODY	Maturity Onset Diabetes of the Young
MSAFP	Maternal Serum Alpha Fetoprotein
mW	molecular Weight
NCBI	National Centre for Biotechnology Information

Ng	nanogram
NGT	Normal Glucose Tolerance
Nm	nanometer
OGTT	Oral Glucose Tolerance Test
p value	probability
PAI-1	Plasminogen Activator Inhibitor-1
pH	Hydrogen Ion concentration
pI	Isoelectric point
PPARγ	Peroxisome Proliferator–Activated Receptor gamma
PTM	Post-Translational Modifications
RAAS	Renin-Angiotensin Aldosterone System
Rpm	revolutions per minute
SDS	Sodium Dodecyl Sulphate
SDS-PAGE	Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis
T1DM	Type 1 Diabetes Mellitus
TCA	Trichloroacetic acid
2-DGE	Two-Dimensional Gel Electrophoresis
T2DM	Type 2 Diabetes Mellitus
USPSTF	U.S. Preventive Service Task Force
µl	Microlitre

UPM	University Putra Malaysia
V	Voltage
V/hr	Voltage per hour
v/v	volume concentration
VDBP	Vitamin D Binding Protein
VDR	Vitamin D Receptor
VDRE	Vitamin D Response Element
VLDL	Very Low Density Lipoprotein
w/v	weight per volume
WHO	World Health Organisation
A	Alpha
B	Beta
Γ	Gamma

CHAPTER 1

INTRODUCTION

1.1 Gestational Diabetes Mellitus

Gestational Diabetes Mellitus (GDM) is defined as any glucose intolerance with onset or first recognition during pregnancy (Buchanan & Xiang, 2005). GDM affects 3 to 14% of pregnancies depending on the population studied. For instance, GDM affects about 14% of the pregnant population in the United States (Jovanovic & Pettitt, 2001). In Malaysia, according to the statistics provided by Hospital Kuala Lumpur in the year 2008, GDM was the most common medical complication and metabolic disorder during pregnancy. There were 3325 new cases of GDM in 2007 while in 2008, 3898 cases were diagnosed (Che Minah, Staff Nurse of Hospital Kuala Lumpur, pers. comm. 20 December 2009).

Generally, the pathophysiology of GDM is still unclear but it is understood that GDM results when the insulin levels are insufficient to meet insulin demands during pregnancy. Placental secretion of hormones such as human Placental Lactogen (hPL), estrogen, progesterone and cortisol is a major contributor to the insulin resistant state seen in pregnancy (Butte, 2000). As pregnancy progresses, the increased placental hormones lead to insulin resistance which prevents glucose from entering the cells and remains in the bloodstream and elevates blood glucose levels to cause GDM. The peak of these hormones is seen from the 26^{th} to 33^{rd} week of gestation (Barros *et al.*, 2006).

The presence of GDM has implications for both the mother and her baby. Prenatal morbidity includes macrosomia, shoulder dystocia, neonatal metabolic abnormalities, congenital malformations and neonatal death which in turn may generate subsequent complications. Long term outcomes for the offspring may include obesity and diabetes independent of genetic factors. For the mother, uncontrolled blood sugar level in expectant mother can lead to preeclampsia, hypertension and cardiovascular diseases during pregnancy. Complications by GDM could lead to caesarean delivery which could add to the length of hospitalisation and there is an increased risk of obvious type 2 diabetes mellitus (T2DM) after pregnancy (Metzenger *et al*., 2007).

The risk factors that contribute to GDM are advancing age, where the age of the expectant mother is more than 35 years old, being overweight or obese, diabetes in their first degree relatives, previous history of GDM and prior delivery to a macrosomic infant (Cho *et al*., 2007).

Screening for glucose intolerance during pregnancy provides an opportunity to offer management to those women diagnosed with GDM and thus reducing maternal morbidity and prenatal morbidity and mortality. The usual approach to detecting GDM is to screen all pregnant women by measuring their plasma glucose by oral glucose tolerance test at 24 to 28 weeks gestation according to World Health Organisation (WHO) guidelines (Maresh, 2005).

Insulin therapy is the most common treatment used to control the blood sugar level among GDM patients. The dose of insulin depends and is tailored to meet each patient's requirement. Self monitoring of blood glucose, diet and exercise are also

recommended to GDM patients in order to keep their blood glucose range at their optimum level (Crowther *et al*., 2005).

1.2 Problem Statement

The main purpose of identifying GDM is to detect women at risk of adverse prenatal outcomes and reduce the serious neonatal complications. It is well recognised that women with previous history of GDM have an increased risk to develop T2DM, which is a major cause of morbidity and mortality and has economic implications as well. The American Diabetes Association (ADA), the American College of Obstetricians and Gynaecologists (ACOG) and the World Health Organisation recommend screening most pregnant women for GDM between 24 and 28 weeks of gestation and screening high risk pregnant women at the first antenatal visit. However, in the year of 2003, the U.S. Preventive Service Task Force (USPSTF) concluded that there was insufficient evidence to advise for or against routinely screening all pregnant women since using clinical risk factors failed to diagnose one third to one half of patients with GDM (Hillier *et al*., 2008).

Even in light of these guidelines, the current diagnostic criteria for GDM remain controversial since the screening approach, prevalence, clinical management and impact on maternal and infant outcomes lack sufficient facts and evidence (Jovanovic & Pettitt, 2001). Many investigators stress the importance of establishing a new criteria for screening that are specific to pregnancy and validated by pregnancy outcomes.

Aside from the lack of international agreement on the diagnosis of GDM, controversy abounds as to the relevance and timing of screening, which would influence management of GDM and affect prenatal outcomes.

1.3 Significance of the study

A major focus of human genetics research is the identification of the molecular basis of diseases as to improve diagnostic capabilities and therapeutic options. Screening for a disease is recommended if the disease is common and clinically important. In addition, also of are about the potential harm and cost of screening especially given the high rates of false-positive or false negative results. In the case of GDM, the purpose of screening is not to diagnose the disease but to identify those at risk as early as reasonably possible for whom a diagnostic test may be offered. Thus, this would provide an opportunity for better health management of those women diagnosed with GDM in the early trimesters.

In order to achieve this goal, the usefulness of a biomarker in screening for complications in pregnancies relies on its detection in maternal blood during the early stages of pregnancy (Shankar *et al*., 2004). These biomarkers could potentially be used as indicators of the effects or progression of GDM. Therefore, a better understanding of the changes that occur at the molecular level in GDM will facilitate early detection of disease. Thus far, no studies have assessed the utility of multiple biomarker screening for GDM in Malaysia.

Proteomic analysis based on mass spectrometry is a powerful tool for the identification of disease-related biomarkers (Shankar *et al*., 2004). With proteomics, profiling of human plasma proteome becomes more feasible in searching for disease related biomarkers in the field of reproduction. The attention of several researchers has focused on the examination of the global protein expression in body fluids in order to provide better diagnosis for GDM and pregnancy related complications.

In the present study, a combined approach based on two-dimensional gel electrophoresis (2-DGE) and tandem mass spectrometry (MS), was used in order to determine differentially expressed proteins for GDM by comparing the protein expression patterns of maternal plasma from normal pregnant women and GDM patients during the different weeks of gestation and to identify a set of GDM specific biomarkers.

Comparative proteome profiling of normal and GDM patients' plasma will contribute significantly to our understanding of the physiology and pathophysiology of GDM. This could translate into identification of disease markers as well as for monitoring of disease progression.

Possibly the most important outcome from this differential proteomic approach is that identified markers could be used to screen patients in the early trimester to reduce the consequences of GDM. In addition, this approach could be the basis in providing a better understanding of GDM especially with regard to underlying molecular pathways involved in GDM progression and potentially lead to novel therapeutic approaches for GDM (Sparre *et al*., 2005).

1.4 Rationale of this study

Identification of differentially expressed proteins in plasma from pregnant woman obtained in early trimester periods as candidate biomarkers for GDM and may potentially provide opportunities for the early detection and treatment of GDM which in turn would help reduce foetal and maternal morbidity and reduce unfavourable outcomes.

1.5 Objectives

1.5.1 General objective:

To identify potential protein markers for GDM.

1.5.2 Specific objectives:

1. To compare the plasma protein profiles for the first, second and third trimesters between GDM patients and normal pregnant women.
2. To compare differentially expressed proteins in plasma between GDM patients and normal pregnant women.
3. To identify potential protein markers in plasma for GDM.

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