Prediction and Risk Assessment of Gestational Diabetes Mellitus (GDM)

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Identification of Proteomic Biomarkers in Maternal Plasma in the Early Second Trimester That Predict the Subsequent Development of Gestational Diabetes

Sun Min Kim, MD[1], Joong Shin Park, MD, PhD[1],
Errol R. Norwitz, MD, PhD[2], Seung Mi Lee, MD[1],
Byoung Jae Kim, MD[1], Chan-Wook Park, MD, PhD[1],
Jong Kwan Jun, MD, PhD[1], Chul-Woo Kim, MD, PhD[3], and
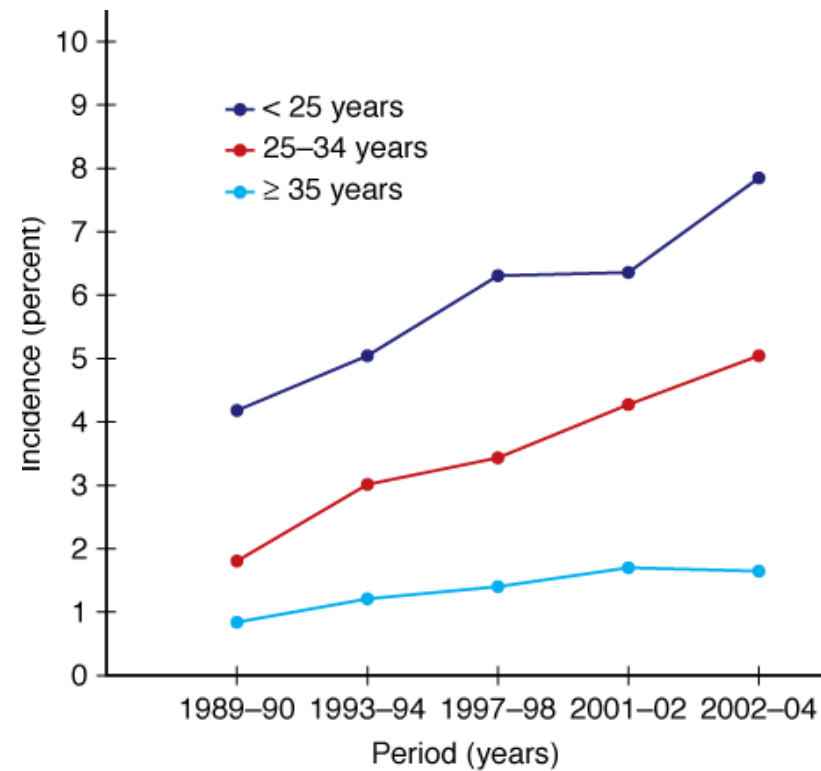Hee Chul Syn, MD, PhD[1]

Abstract

Introduction: This study is designed to identify proteomic biomarkers that predict the subsequent development of gestational diabetes mellitus (GDM). Methods: Maternal blood was obtained prospectively from healthy pregnant women in the early second trimester (16-20 weeks). Twelve women subsequently diagnosed with GDM at 24 to 28 weeks were selected as cases; an equal number of normoglycemic women as controls. Proteomic analysis of the previously stored plasma was performed by surface-enhanced laser desorption/ionization time-of-flight (SELDI-TOF) mass spectrometry. Results: Three peaks (9122 Da, 9412 Da, and 9701 Da) that were increased in cases were characterized as isoforms of apolipoprotein CIII. Another discriminatory peak (17 105 Da) that was decreased in cases was matched to apolipoprotein AII. Enzyme-linked immunosorbent assay (ELISA) confirmed that women who subsequently developed GDM had significantly higher levels of apolipoprotein CIII than controls did. Levels of apolipoprotein AII failed to reach statistical significance. Conclusion: Our data suggest that there already exist biomarkers in the maternal circulation at 16 to 20 weeks in women who subsequently develop GDM.
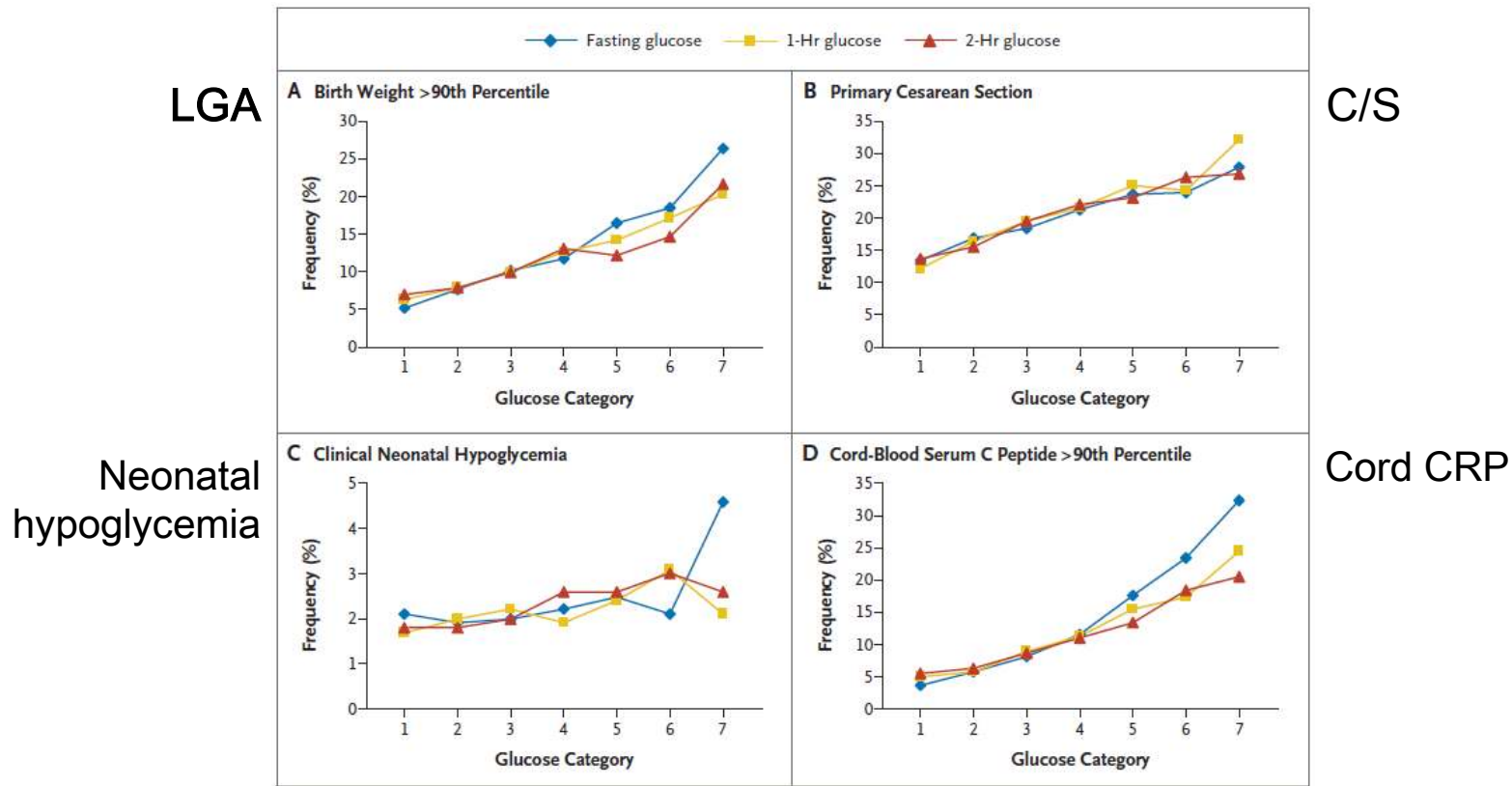
Increase of incidence of GDM

• Age-specific incidence of GDM

(Getahun et al. AJOG. 2008)

HAPO study
Frequency of Adverse Outcomes across the Glucose Categories

LGA

C/S

Neonatal hypoglycemia

Cord CRP
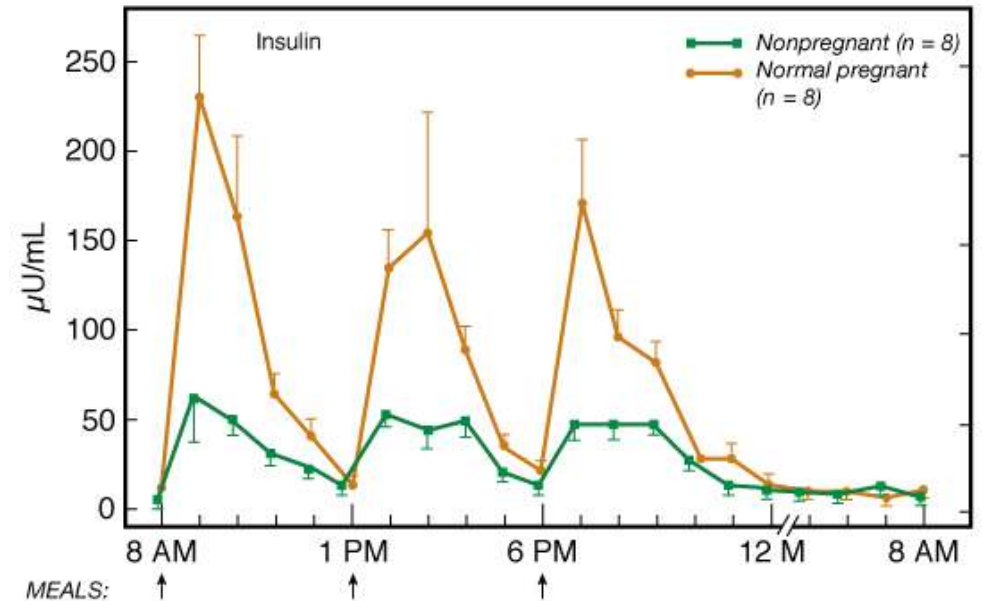
(NEJM 2008;358:1991-2002)

Diurnal changes in plasma glucose and insulin in normal late pregnancy

Glucose

Insulin

(Phelps et al. Am J Obstet Gynecol 1981)
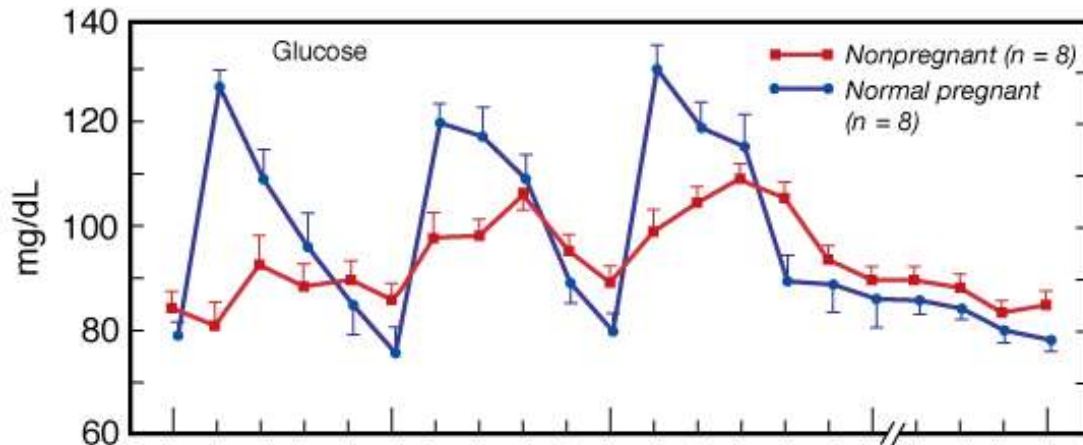
Maternal serum concentrations of human placental lactogen (hPL) during pregnancy
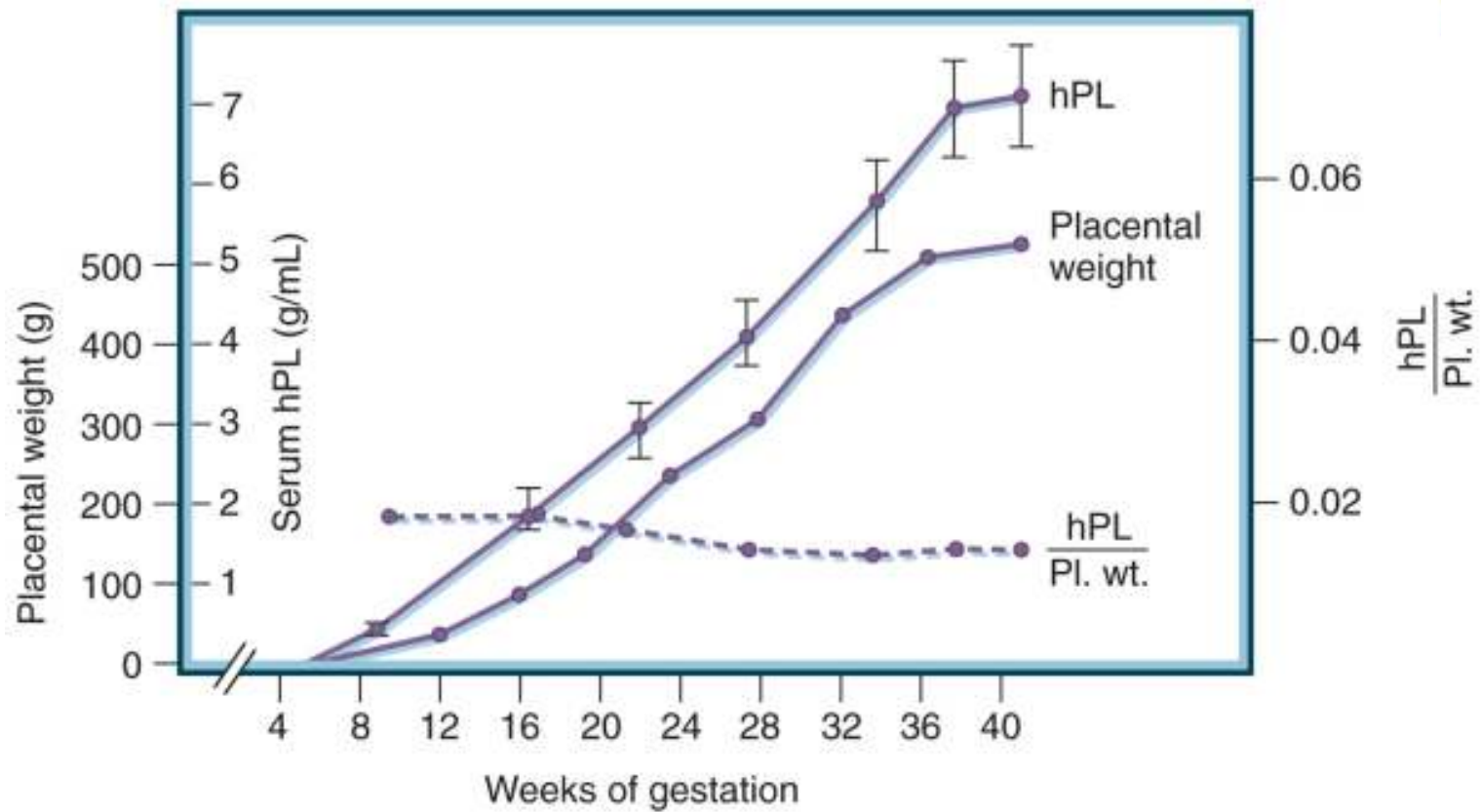
Definition of GDM
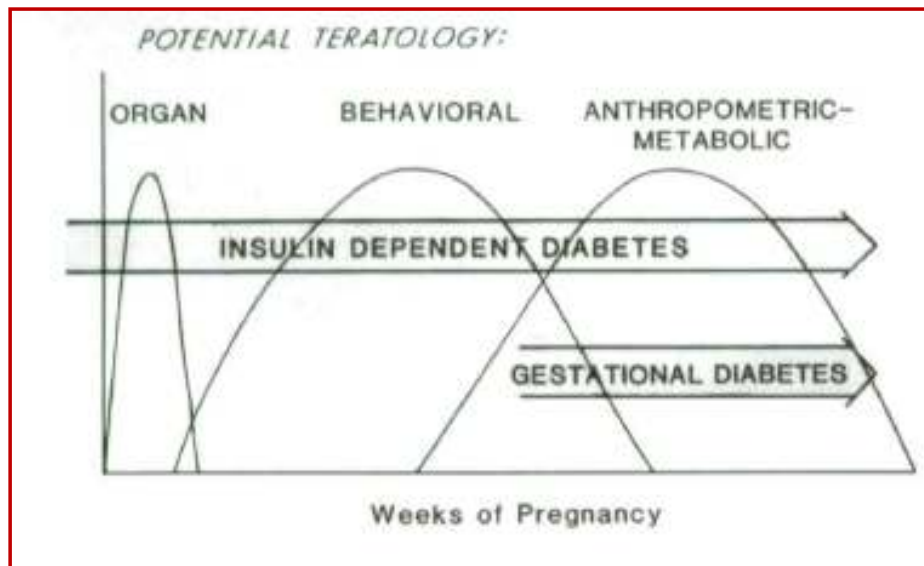
Carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy

Third International Workshop-Conference on GDM, 1991
ACOG Practice Bulletin, 2001

GDM is a heterogeneous entity

GDM includes

Pregnancy-induced glucose intolerance &
Previously undiagnosed overt diabetes discovered during pregnancy

Fifth International Workshop-Conference on Gestational Diabetes: Recommended Screening Strategy Based on Risk Assessment for Detecting Gestational Diabetes (GDM)

GDM risk assessment: Should be ascertained at the first prenatal visit

•**Low Risk:** Blood glucose testing not routinely required if all the following are present:
  —Member of an ethnic group with a low prevalence of GDM
  —No known diabetes in first-degree relatives
  —Age < 25 years
  —Weight normal before pregnancy
  —Weight normal at birth
  —No history of abnormal glucose metabolism
  —No history of poor obstetrical outcome

•**Average Risk:** Perform blood glucose testing at 24 to 28 weeks using either:
  —Two-step procedure: 50-g oral glucose challenge test (GCT), followed by a diagnostic 100-g oral glucose tolerance test for those meeting the threshold value in the GCT.
  —One–step procedure: Diagnostic 100-g oral glucose tolerance test performed on all subjects.

•**High Risk:** Perform blood glucose testing as soon as feasible, using the procedures described above if one or more of these are present:
  —Severe obesity
  —Strong family history of type 2 diabetes
  —Previous history of GDM, impaired glucose metabolism, or glucosuria. If GDM is not diagnosed, blood glucose testing should be repeated at 24 to 28 weeks or at any time there are symptoms or signs suggestive of hyperglycemia.

Proportion of detection for GDM during early pregnancy

Between 40% and 66% of cases of so-called gestational diabetes could be detected during early pregnancy

(J Reprod Med 1996; 41: 675-9)

(Diabetes Care 1991; 14: 288-94)

Gestational diabetes mellitus diagnosed during early pregnancy

Jose L. Bartha, MD, Pilar Martinez-Del-Fresno, MD, and Rafael Comino-Delgado, MD

Puerto Real, Spain

Do women with GDM diagnosed during early pregnancy have a higher risk than do those in whom GDM emerges during late pregnancy?

50gGCT at the first antenatal visit
(n=3986)

GDM
(n=65)

Within normal limit

VS

50gGCT at 24-28 weeks of gestation

GDM
(n=170)

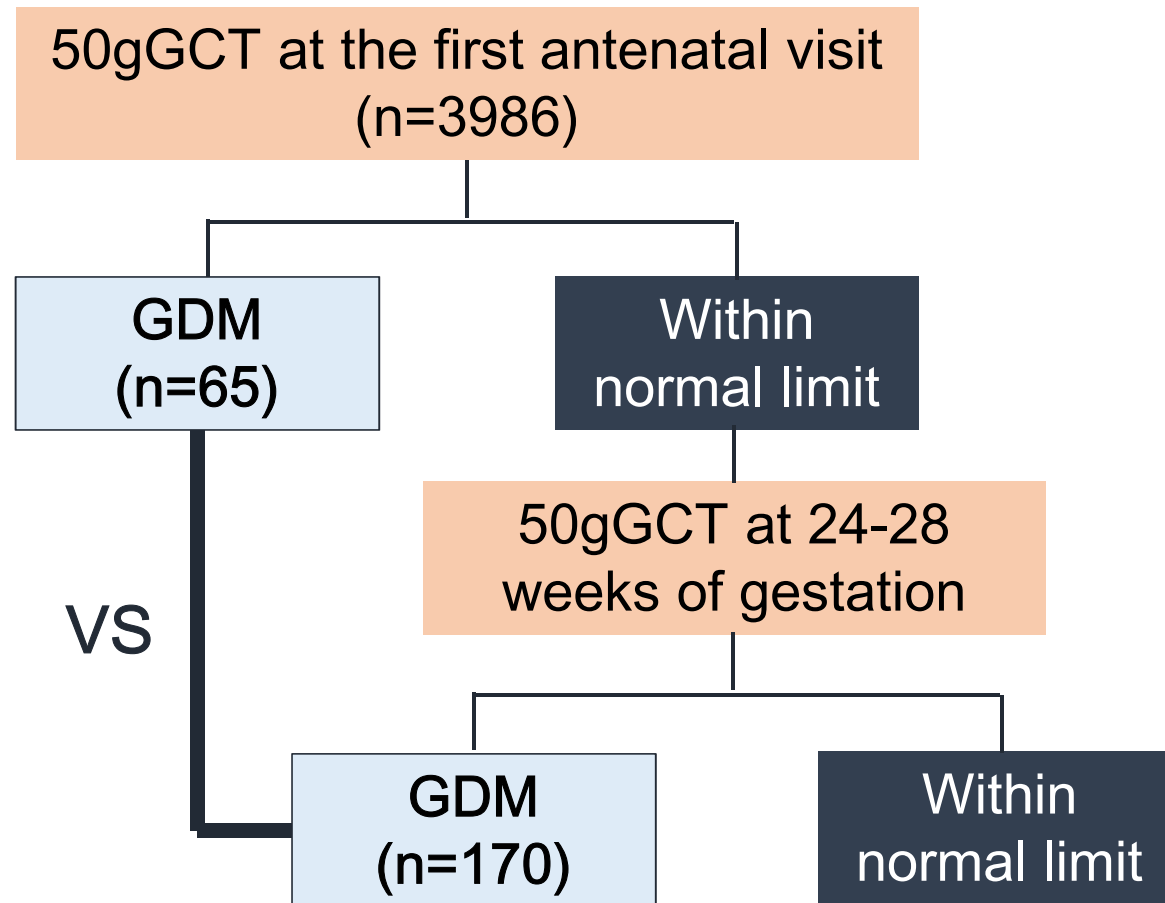Within normal limit

(AJOG 2000; 182: 346-50)

Gestational diabetes mellitus diagnosed during early pregnancy

Jose L. Bartha, MD, Pilar Martinez-Del-Fresno, MD, and Rafael Comino-Delgado, MD

Puerto Real, Spain

Table II. Pregnancy complications

	Early-onset gestational diabetes (n = 65)		Late-onset gestational diabetes (n = 170)		Statistical signifi
	No.	%	No.	%	
Hypertension (total)	12	18.5	10	5.9	P = .006
Chronic hypertension	7	10.8	4	2.4	P = .01
Preeclampsia	2	3.1	0	0	P = .07
Superimposed preeclampsia	2	3.1	1	0.6	NS
Total preeclampsia (preeclampsia plus superimposed preeclampsia)	4	6.2	1	0.6	P = .02
Gestational hypertension	1	1.5	5	2.9	NS
Hydramnios	2	3.1	7	4.1	NS
Preterm labor	2	3.1	6	3.5	NS
Fetal anomalies	0	0	0	0	NS
Oligohydramnios	0	0	11	6.47	P = .02

Gestational diabetes mellitus diagnosed during early pregnancy

Jose L. Bartha, MD, Pilar Martinez-Del-Fresno, MD, and Rafael Comino-Delgado, MD

Puerto Real, Spain

Table III. Glycemic control and insulin therapy

	Early-onset gestational diabetes (n = 65)	Late-onset gestational diabetes (n = 170)	Statistical significance
Fasting glucose level (mg/dL, mean ± SD)	91.4 ± 16.1	79.8 ± 14.2	$P < .00001$
Glucose level after breakfast (mg/dL, mean ± SD)	104.6 ± 29.3	95.9 ± 20.6	$P = .03$
Glucose level after lunch (mg/dL, mean ± SD)	102.6 ± 19.4	91.57 ± 16.2	$P = .00009$
Glucose level before dinner (mg/dL, mean ± SD)	82.1 ± 17.3	77.1 ± 14.6	$P = .039$
Glucose level after dinner (mg/dL, mean ± SD)	102.8 ± 26.0	93.7 ± 17.3	$P = .01$
Mean glycemic profile (mg/dL, mean ± SD)	96.7 ± 15.0	87.6 ± 10.4	$P = .00002$
Glycosylated hemoglobin (%, median and interquartile range)	4.5 (4.2-5.2)	4.6 (4.3-4.9)	NS
Insulin therapy (No.)	22/65 (33.9%)	12/170 (7.1%)	$P < .00001$

NS, Not significant.

Gestational diabetes mellitus diagnosed during early pregnancy

Jose L. Bartha, MD, Pilar Martinez-Del-Fresno, MD, and Rafael Comino-Delgado, MD

Puerto Real, Spain

Table IV. Obstetric and neonatal outcomes

	Early-onset gestational diabetes (n = 50)	Late-onset gestational diabetes (n = 133)	Statistical significa
Vaginal births	38 (76%)	107 (80.5%)	NS
Cesarean deliveries for fetal distress	1 (8.3%)	2 (7.7%)	NS
Cesarean deliveries for fetopelvic disproportion	4 (33.3%)	12 (46.2%)	NS
Cesarean deliveries for failed induction	1 (8.3%)	1 (3.9%)	NS
Gestational age at birth (wk, mean ± SD)	39.0 ± 2.7	39.3 ± 1.7	NS
Preterm births	3 (6%)	7 (5.3%)	NS
5-min Apgar score <7	1 (2%)	4 (3.0%)	NS
1-min Apgar score <6	6 (12%)	6 (4.5%)	NS
Neonatal weight (g, mean ± SD)	3419.6 ± 643.3	3281.4 ± 580.9	NS
Small for gestational age	5 (10%)	20 (15.0%)	NS
Macrosomia (>4000 g)	7 (14%)	11 (8.3%)	NS
Meconium passage	9 (23.1%)	24 (21.8%)	NS
Special care baby unit admission	5 (10%)	14 (10.5%)	NS
Neonatal hypoglycemia	4 (8%)	0 (0%)	$P = .005$
Low birth weight (<2500 g)	0 (0%)	6 (4.5%)	NS
Perinatal deaths	3 (6%)	0 (0%)	$P = .02$

NS, Not significant.

Gestational diabetes mellitus diagnosed during early pregnancy

Jose L. Bartha, MD, Pilar Martinez-Del-Fresno, MD, and Rafael Comino-Delgado, MD

Puerto Real, Spain

Women with an early diagnosis of gestational diabetes represent a high-risk subgroup

Early diagnosis of gestational diabetes mellitus and prevention of diabetes-related complications

Jose L. Bartha , Pilar Martinez-Del-Fresno, Rafael Comino-Delgado

Department of Obstetrics and Gynaecology, University Hospital of Puerto Real, Carretera Nacional IV, KM 665, 11150 Puerto Real, Cádiz, Spain

Could early diagnosis of GDM avoid some diabetes-related complications?

Early diagnosis of gestational diabetes mellitus and prevention of diabetes-related complications

Jose L. Bartha , Pilar Martinez-Del-Fresno, Rafael Comino-Delgado

Department of Obstetrics and Gynaecology, University Hospital of Puerto Real, Carretera Nacional IV, KM 665, 11150 Puerto Real, Cádiz, Spain

Later screening group (n=189)

50g glucose screening at 24-28 weeks of gestation to 3504 consecutive pregnant women From May 1994 to February 1996

VS

Early screening group (n=235)

50g glucose screening at the time of their first antenatal visit to 3986 consecutive pregnant women From March 1996 to March 1998

Early diagnosis of gestational diabetes mellitus and prevention of diabetes-related complications

Fresno, Rafael Comino-Delgado
al, Carretera Nacional IV, KM 665, 11150 Puerto Real, Cádiz, Spain

Table 2
Pregnancy complications

	Later screening group ($n = 189$)	Earlier screening group ($n = 235$)	P^a
Hypertension (total)	19 (10.0)	22 (9.4)	ns
Chronic hypertension	8 (4.2)	11 (4.7)	ns
Preeclampsia	4 (2.1)	2 (0.8)	ns
Superimposed preeclampsia	1 (0.5)	3 (1.3)	ns
Total of preeclampsia (preeclampsia + superimposed preeclampsia)	5 (2.6)	5 (2.1)	ns
Gestational hypertension	6 (3.2)	6 (2.5)	
Hydramnios	24 (12.7)	5 (2.1)	<0.001
Preterm premature rupture of membranes	4 (2.1)	0 (0)	0.03
Fetal anomalies	6 (3.2)	0 (0)	0.007
Oligohydramnios	7 (3.7)	11 (4.6)	ns

The values given in parentheses represent percentage.
[a] ns: not significant.

Hydramnios 24(12.7%) vs 5(2.1%) (P<0.001)

(Eur J Obstet Gynecol Reprod Biol 2003;109:41-44)

Early diagnosis of gestational diabetes mellitus and prevention of diabetes-related complications

z-Del-Fresno, Rafael Comino-Delgado

Puerto Real, Carretera Nacional IV, KM 665, 11150 Puerto Real, Cádiz, Spain

Table 4
Obstetric and perinatal outcomes

	Later screening group ($n = 169$)	Earlier screening group ($n = 183$)	P^a
Vaginal births	132 (78.1)	145 (79.2)	ns
Cesarean section for fetal distress	4 (2.4)	3 (1.6)	ns
Cesarean section for disproportion	8 (4.73)	16 (8.74)	ns
Cesarean section for failed induction	2 (1.2)	2 (1.1)	ns
Gestational age at birth	38.8 ± 1.9	39.3 ±	
Preterm births	20 (11.8)	10 (5.5)	0.03
Apgar's score <7, 5 min	7 (4.1)	5 (2.7)	ns
Apgar's score <6, 1 min	10 (5.9)	12 (6.5)	ns
Newborn weight (g)	3314.0 ± 530.4	3319.2 ± 600.0	ns
Small-for-gestational-age	10 (5.9)	25 (13.7)	0.02
Macrosomia (>4000 g)	13 (7.7)	18 (9.8)	ns
Meconium passage	42 (24.8)	33 (18.0)	ns
Special Care Baby Unit	28 (16.6)	19 (10.4)	ns
Neonatal hypoglycemia	4 (2.4)	4 (2.2)	ns
Low birthweight (<2500 g)	14 (8.3)	6 (3.3)	ns
Perinatal mortality	3 (1.8)	3 (1.6)	ns

The values given in parentheses represent percentage.
[a] ns: not significant.

Preterm births 20(11.8%) vs 10(5.5%) (P=0.03)

(Eur J Obstet Gynecol Reprod Biol 2003;109:41-44)

Early diagnosis of gestational diabetes mellitus and prevention of diabetes-related complications

Jose L. Bartha[*], Pilar Martinez-Del-Fresno, Rafael Comino-Delgado

Department of Obstetrics and Gynaecology, University Hospital of Puerto Real, Carretera Nacional IV, KM 665, 11150 Puerto Real, Cádiz, Spain

- Early glucose tolerance screening could avoid some diabetes-related complications in women with gestational diabetes

- However, further studies are needed to know if it should be done in all pregnant women or only in those with a high risk of developing diabetes

(Eur J Obstet Gynecol Reprod Biol 2003;109:41-44)

Previous studies about prediction or early diagnosis of GDM during pregnancy

Estimating the risk of gestational diabetes mellitus: a clinical prediction model based on patient characteristics and medical history

M van Leeuwen,[a] BC Opmeer,[b] EJK Zweers,[c,d] E van Ballegooie,[e,*] HG ter Brugge,[f] HW de Valk,[d] GHA Visser,[g] BWJ Mol[a,g]

(BJOG 2010;117:69-75)

Original Article

Gestational diabetes: Development of an early risk prediction tool to facilitate opportunities for prevention

Helena J. TEEDE,[1,2,3] Cheryce L. HARRISON,[1,2] Wan T. TEH,[3] Eldho PAUL[1] and Carolyn A. ALLAN[2,3]

(Aust N Z J Obstet Gynaecol 2011;51:499-504)

Previous studies about prediction or early diagnosis of GDM during pregnancy

DOI: 10.1111/j.1464-5491.2005.01634.x

Prediction of gestational diabetes mellitus in a high-risk group by insulin measurement in early pregnancy

T. Bitó, I. Földesi, T. Nyári* and A. Pál

Previous studies about prediction or early diagnosis of GDM during pregnancy

PLOS | ONE

Maternal Serum Heme-Oxygenase-1 (HO-1) Concentrations in Early Pregnancy and Subsequent Risk of Gestational Diabetes Mellitus

Chunfang Qiu[1]*, Karin Hevner[1], Daniel A. Enquobahrie[1,2], Michelle A. Williams[1,3]

1 Center for Perinatal Studies, Swedish Medical Center, Seattle, Washington, United States of America, 2 Department of Epidemiology, University of Washington School of Public Health, Seattle, Washington, United States of America, 3 Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America

Serum HO-1 concentration according to GDM case-control status
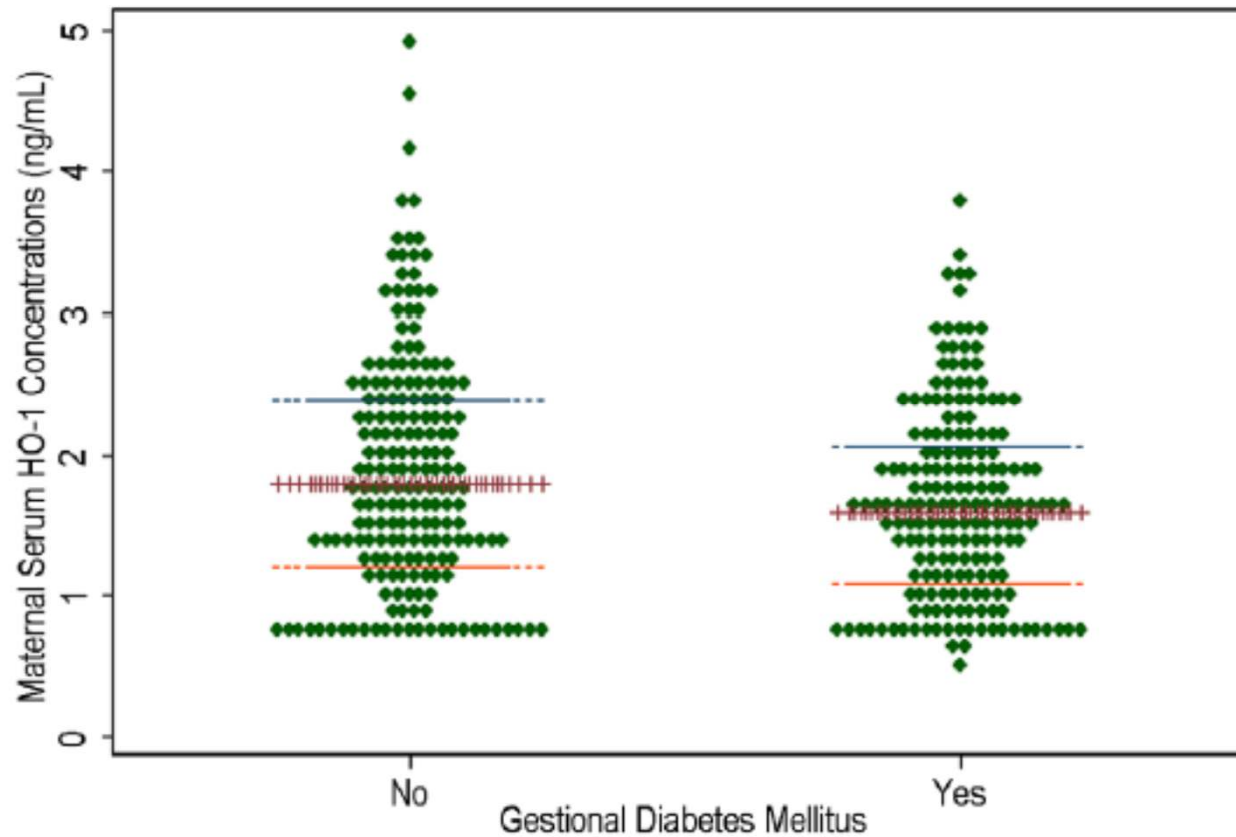
Previous studies about prediction or early diagnosis of GDM during pregnancy

First-Trimester Prediction of Gestational Diabetes Mellitus: Examining the Potential of Combining Maternal Characteristics and Laboratory Measures

Makrina Savvidou,[1] Scott M. Nelson,[2] Mahlatse Makgoba,[1] Claudia-Martina Messow,[2] Naveed Sattar,[2] and Kypros Nicolaides[3]

Previous studies about prediction or early diagnosis of GDM during pregnancy

Prediction of gestational diabetes mellitus by maternal factors and biomarkers at 11 to 13 weeks[†]

Surabhi Nanda[1], Mina Savvidou[1], Argyro Syngelaki[1], Ranjit Akolekar[1] and Kypros H. Nicolaides[1,2]*

(Prenat Diagn 2011;31:135-141)

Objective

Identification of biomarkers that predict the subsequent development of GDM
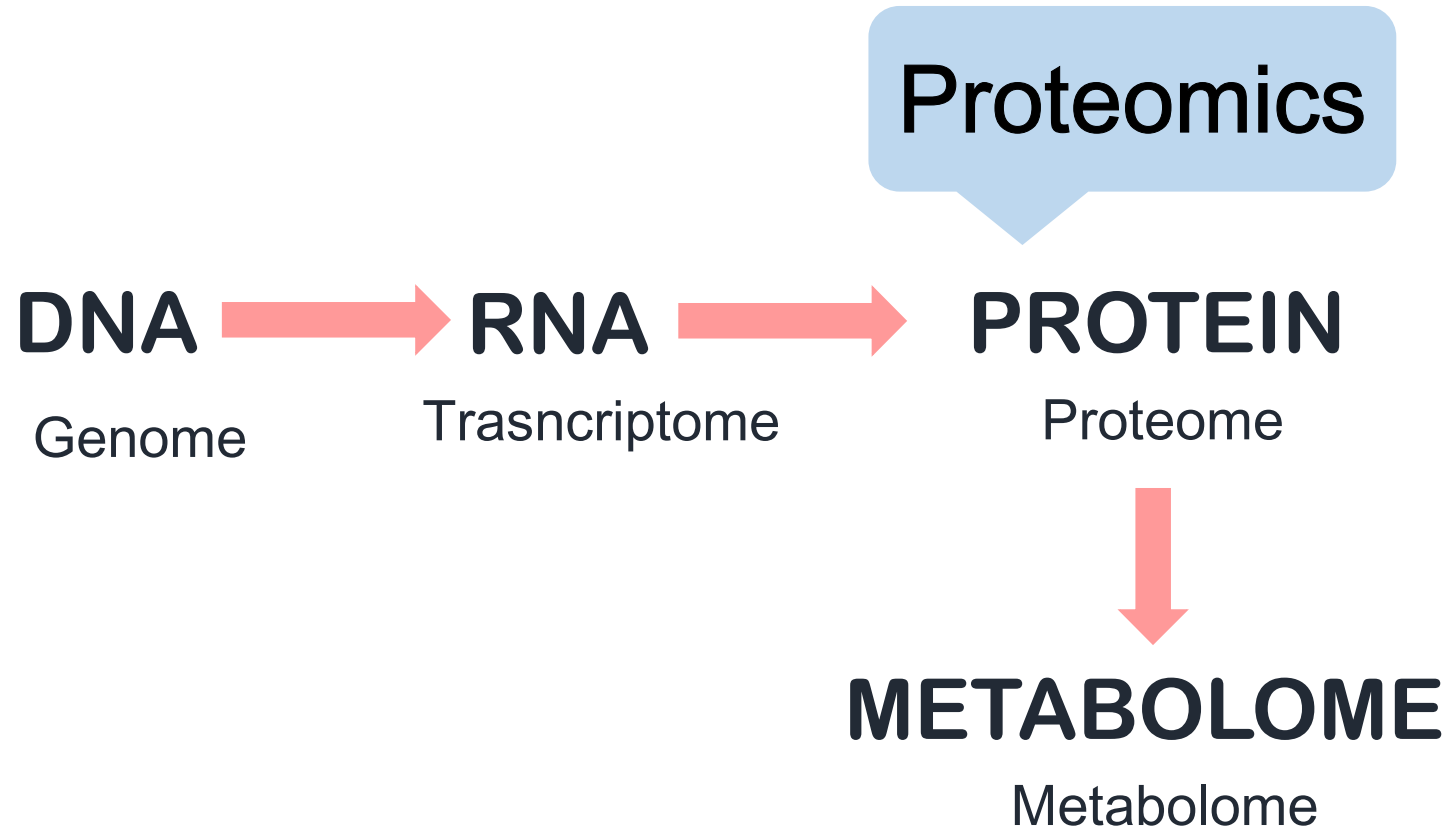
Clinical Proteomics Workflow for biomarker discovery

Biological specimens

Proteomic analysis

Proteome analysis

Improved diagnosis and therapy
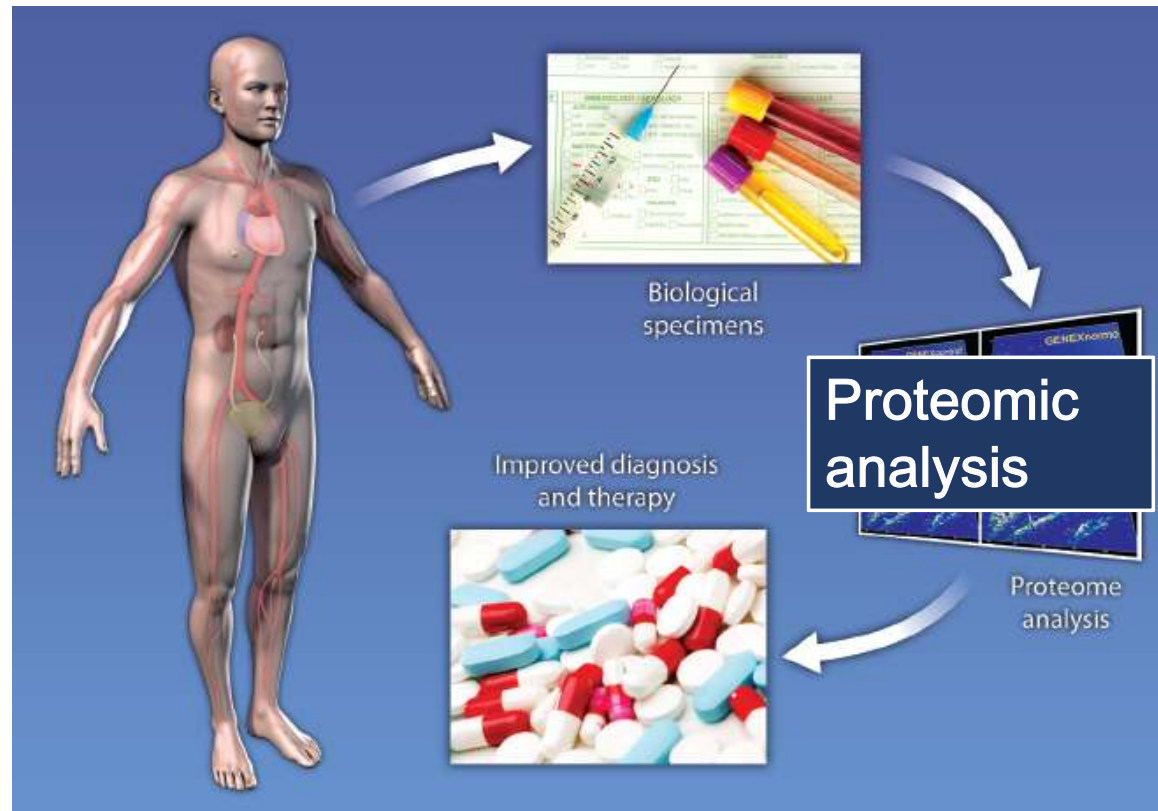
(Mischak et al. Sci Transi Med 2010)

Central dogma

DNA → RNA → PROTEIN

Transcription

Translation

Replication
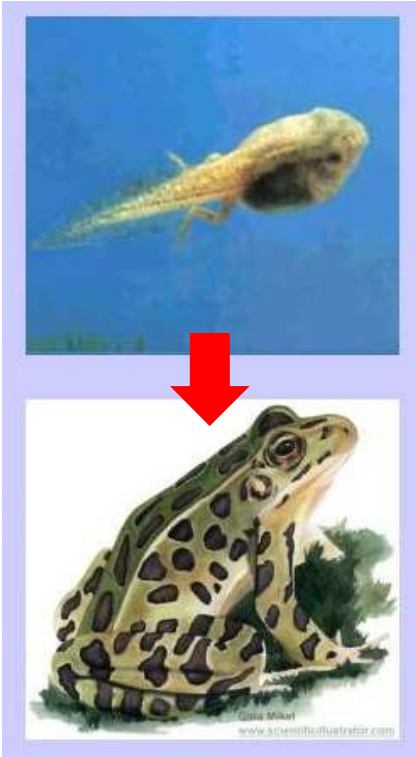
by Francis Crick (1958)
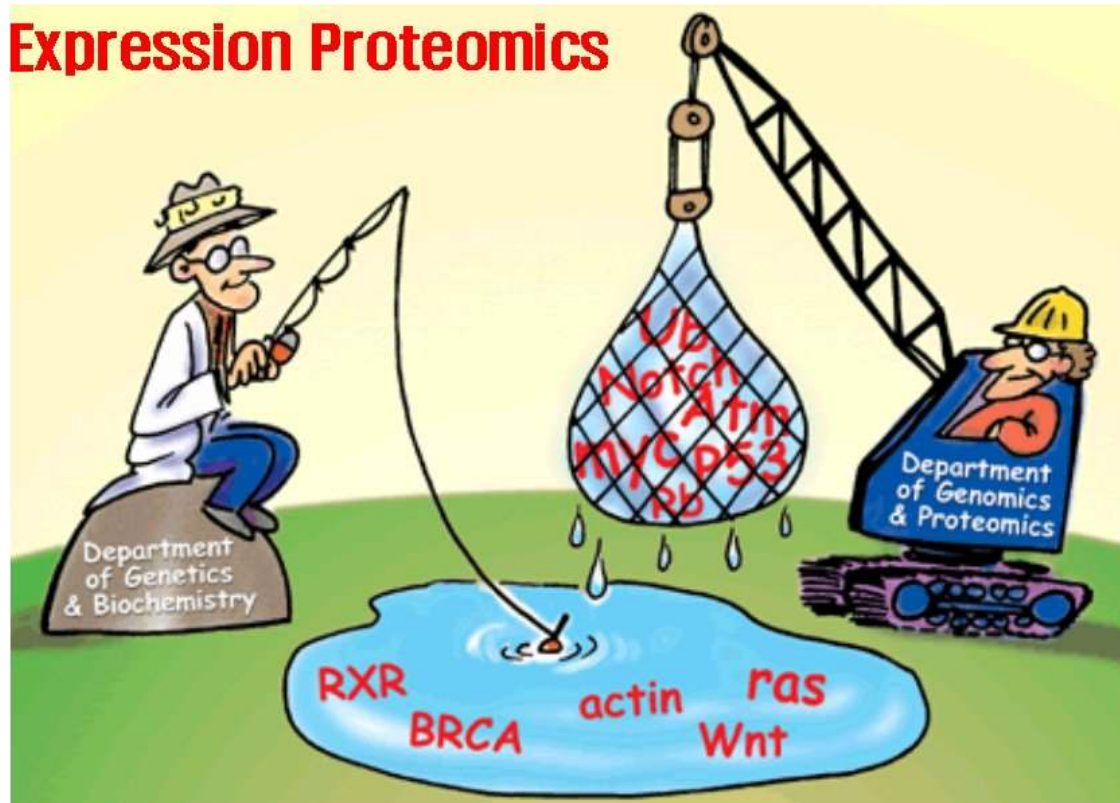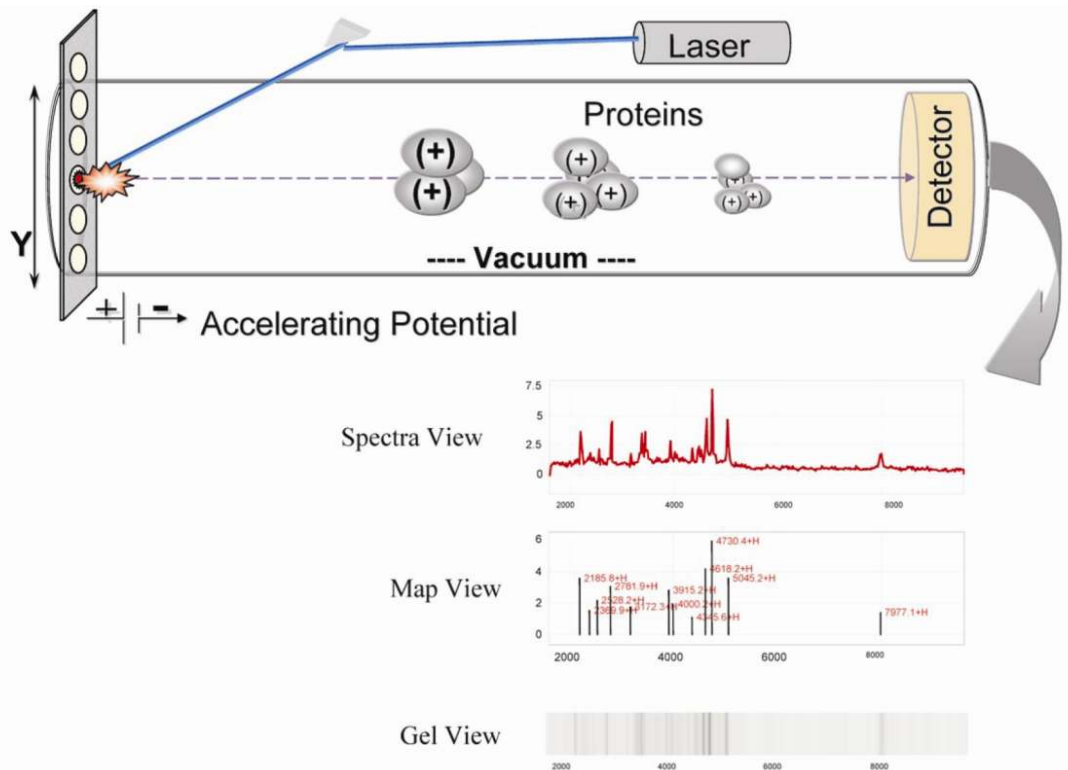
Why proteomics?

Objective

To identify biomarkers that predict the subsequent development of GDM using proteomics
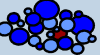
SELDI-TOF-MS
(Surface-enhanced laser desorption/ionization time-of-flight mass spectrometry)

- High-throughput proteomic technique

- Small amount of starting material

- Rapid and reproducible protein profile

(Biochem Biophys Res Commun 2002;292:587-92)

The SELDI ProteinChip® Process and Arrays

1. Sample goes *directly* onto the ProteinChip Array
2. Proteins are captured, retained and purified directly on the chip (affinity capture)
3. Surface is "read" by Surface-Enhanced Laser Desorption/Ionization (SELDI)

Laser

Molecular Weight

Sample

$100\ \mu m^2$
to
$1\ mm^2$

ProteinChip Array

Chemical, Biochemical or Biological Capture Surface
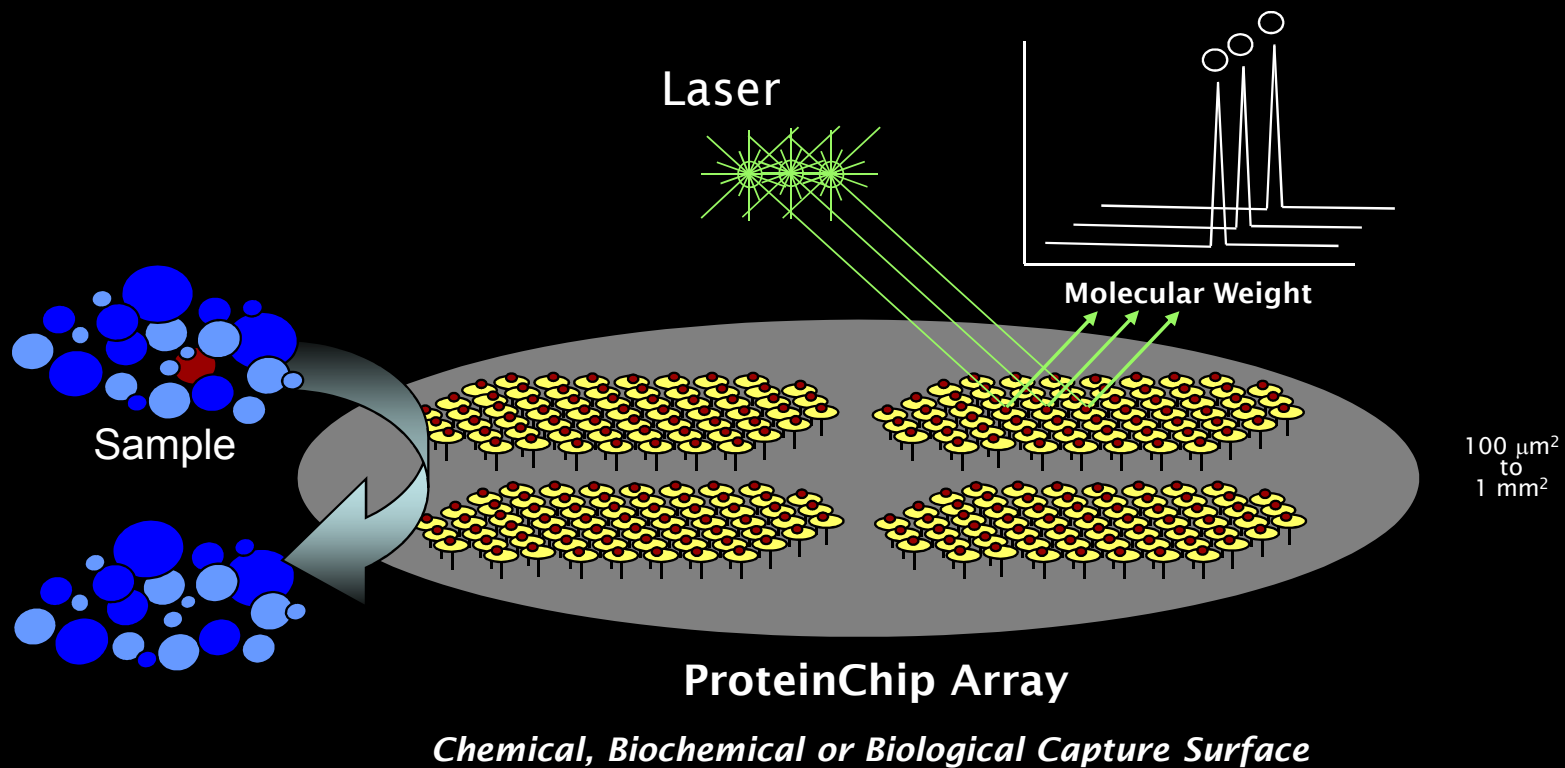
Materials and Methods

- Patients and samples

    - Healthy singleton pregnancy

    - Maternal blood collection in the early second trimester (16-20 weeks of gestation)

    - Centrifuge (at 700 x g for 10 minutes) and the supernatant in polypropylene tubes at -70˚C until assay

Materials and Methods

- GDM screening: between 24 and 28 weeks of gestation using a 1-hour nonfasting 50-g oral glucose challenge test

- GDM diagnosis: on a 3-hour 100-g oral glucose tolerance test using the Carpenter and Coustan criteria

Materials and Methods

- Case: Women subsequently diagnosed with GDM

- Controls: Normoglycemic women matched for age, parity, gestational age at blood sampling, and BMI

Proteomic analysis process
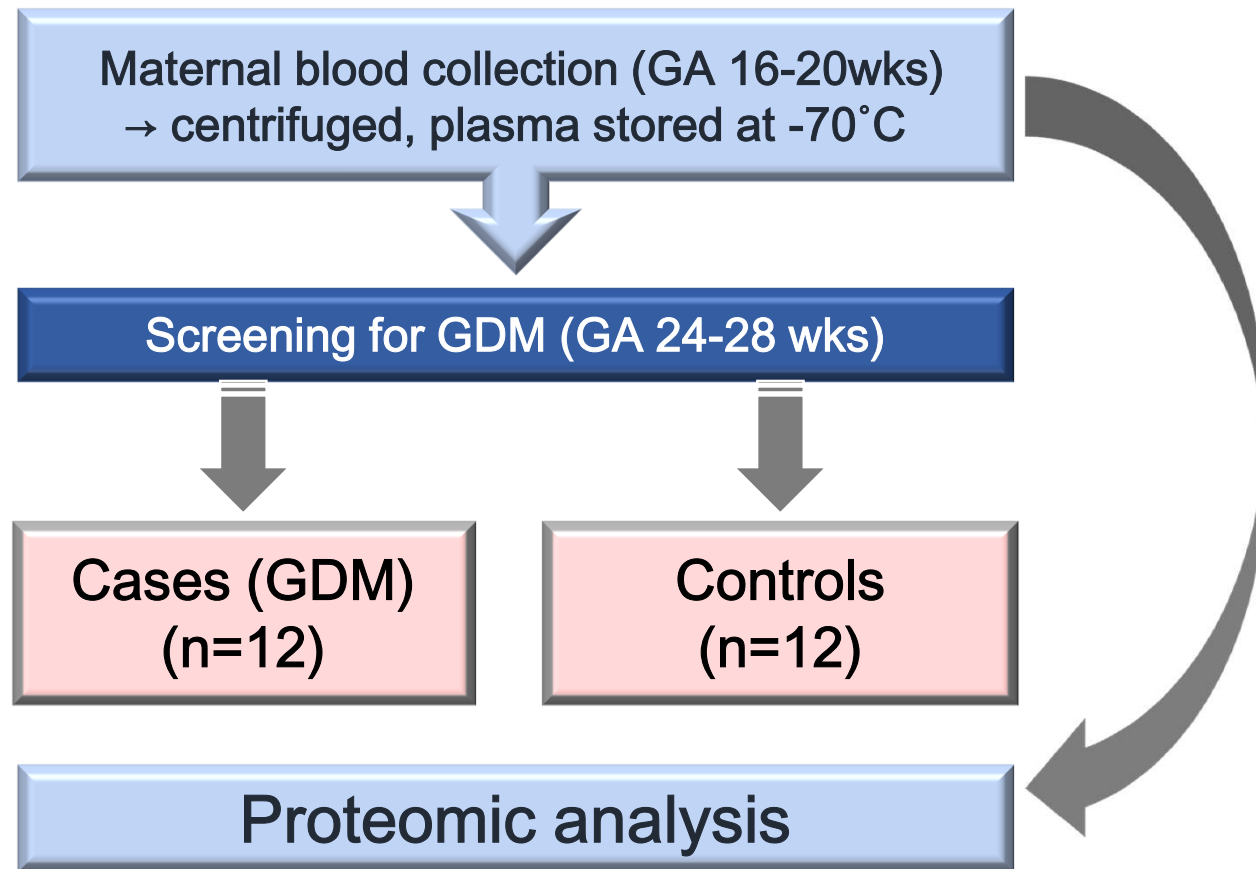
I. Protein profiling (SELDI-TOF MS)

II. Isolation
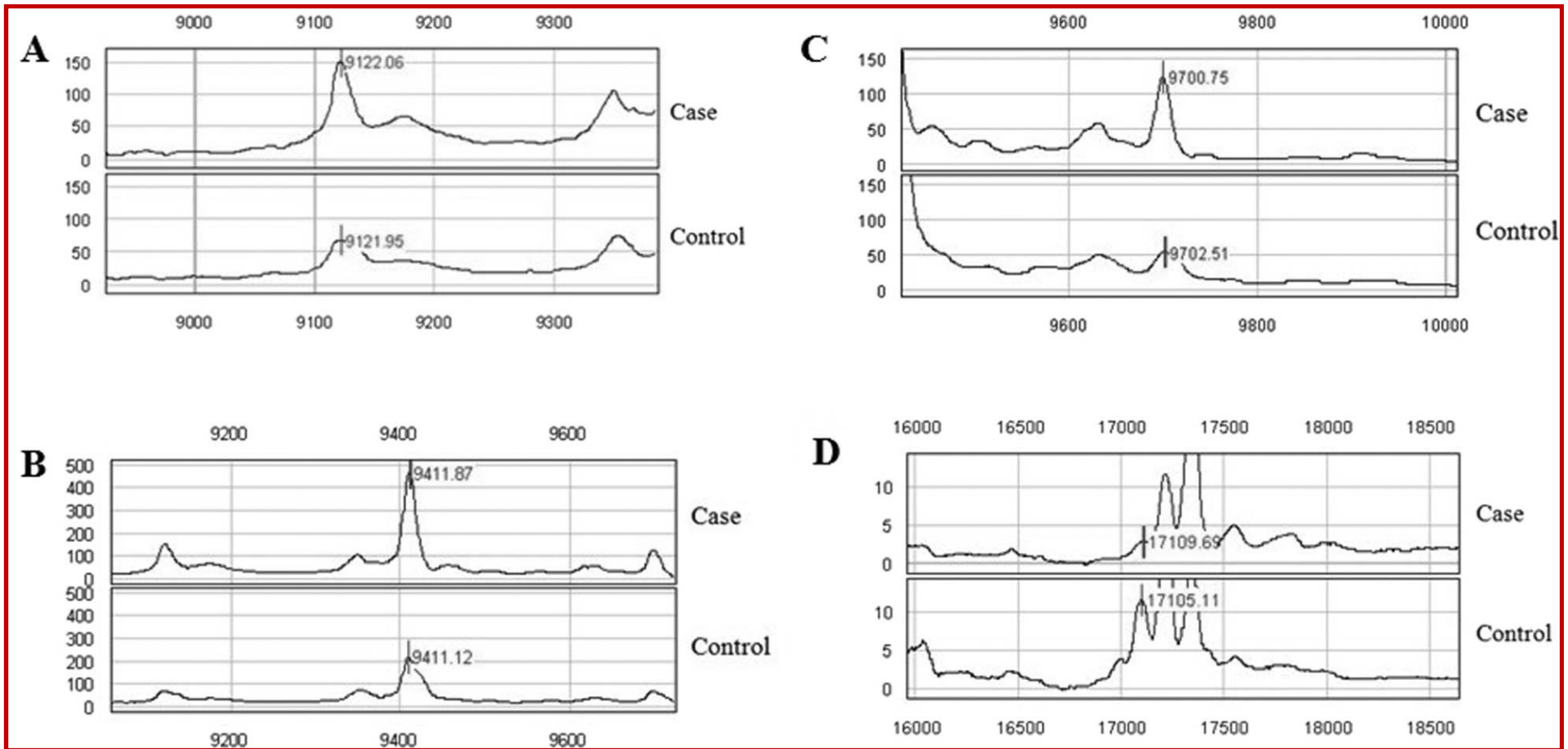
III. Identification

IV. Validation (immunodepletion)

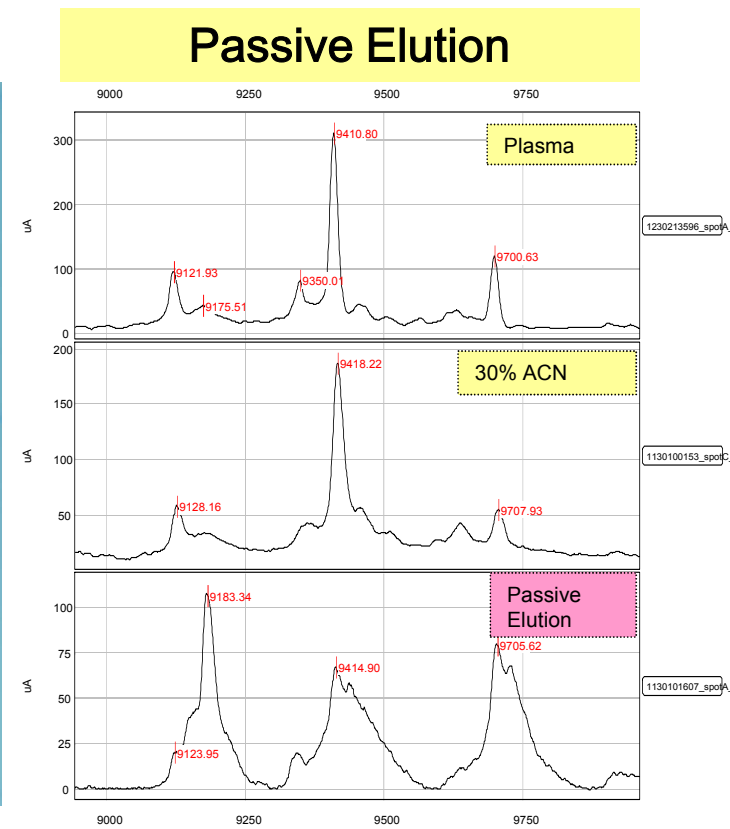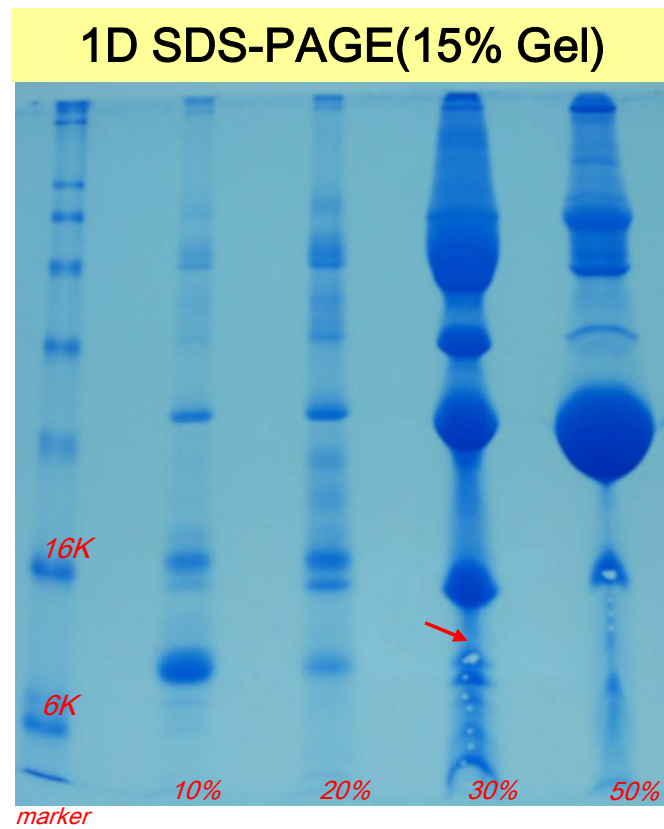V. Quantification (ELISA)

Workflow

Results

Protein profiling

Purification and separation of protein peaks of interest

Identification

{MATRIX SCIENCE} Mascot Search Results

Apolipoprotein C-III

Protein View

Match to: gi|186972736 Score: 135
Chain A, Structure And Dynamics Of Human Apolipoprotein C-Iii
Found in search of D:\PE Sciex Data\Mascot\mas34.tmp

Nominal mass (M_r): 8759; Calculated pI value: 4.72
NCBI BLAST search of gi|186972736 against nr
Unformatted sequence string for pasting into other applications

Taxonomy: Homo sapiens
Links to retrieve other entries containing this sequence from NCBI Entrez:
gi|224917 from Homo sapiens

Fixed modifications: Carbamidomethyl (C)
Variable modifications: Oxidation (M)
Cleavage by Trypsin: cuts C-term side of KR unless next residue is P
Sequence Coverage: 41%

Matched peptides shown in Bold Red

```
    1 SEAEDASLLS FMQGYMKHAT KTAKDALSSV QESQVAQQAR GWVTDGFSSL
   51 KDYWSTVKDK FSEFWDLDPE VRPTSAVAA
```

[Show predicted peptides also]

[Sort Peptides By]   ⊙ Residue Number ○ Increasing Mass ○ Decreasing Mass

Start - End	Observed	Mr(expt)	Mr(calc)	Delta	Miss	Sequence	
1 - 17	953.8000	1905.5854	1905.8488	-0.2634	0	-.SEAEDASLLSFMQGYMK.H	(Ions score 71)
25 - 40	858.8000	1715.5854	1715.8438	-0.2584	0	K.DALSSVQESQVAQQAR.G	(Ions score 65)

Purification and separation of protein peaks of interest

Identification

Apolipoprotein A-II

{MATRIX SCIENCE} **Mascot Search Results**

Protein View

Match to: gi|24987503 Score: 73
Chain A, Structures Of Apolipoprotein A-Ii And A Lipid Surrogate Complex Provide Insights Into Apolipoprotein-Lipid Interactions
Found in search of D:\PE Sciex Data\Mascot\mas36.tmp

Nominal mass (M_r): 8759; Calculated pI value: 5.05
NCBI BLAST search of gi|24987503 against nr
Unformatted sequence string for pasting into other applications
Fixed modifications: Carbamidomethyl (C)
Variable modifications: Oxidation (M)
Cleavage by Trypsin: cuts C-term side of KR unless next residue is P
Sequence Coverage: 41%

Matched peptides shown in Bold Red

```
 1  QAKEPCVESL VSQYFQTVTD YGKDLMEKVK SPELQAEAKS YFEKSKEQLT
51  PLIKKAGTEL VNFLSYFVEL GTQPATQ
```
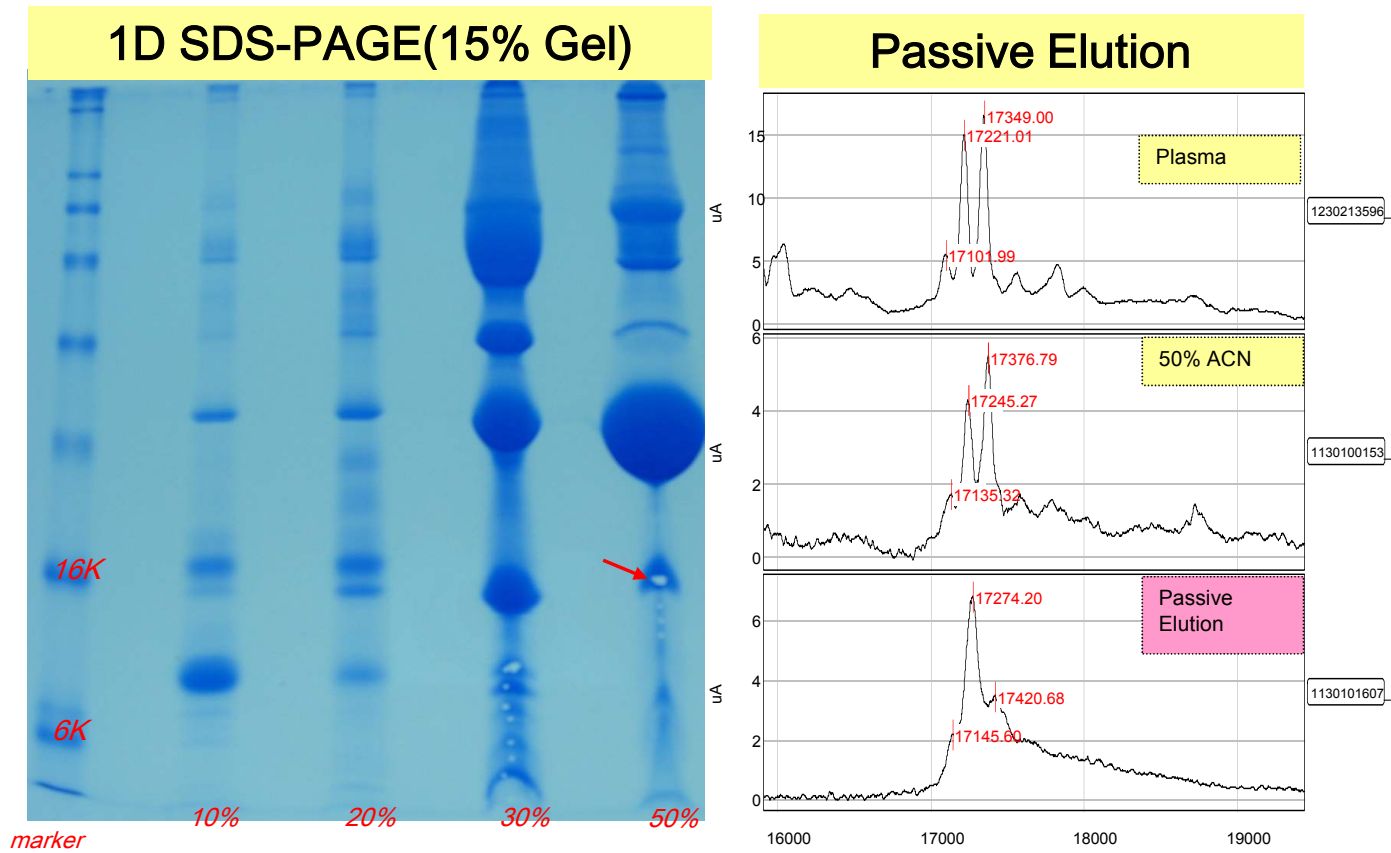
[Show predicted peptides also]

[Sort Peptides By] ⦿ Residue Number ◯ Increasing Mass ◯ Decreasing Mass

Start - End	Observed	Mr(expt)	Mr(calc)	Delta	Miss	Sequence	
45 - 54	578.8000	1155.5854	1155.6863	-0.1008	1	K.SKEQLTPLIK.K	(Ions score 35)
56 - 77	795.7000	2384.0782	2384.1900	-0.1118	0	K.AGTELVNFLSYFVELGTQPATQ.-	(Ions score 38)

Antibody validation – Apolipoprotein CIII

Different isoforms of Apo A-II in human plasma
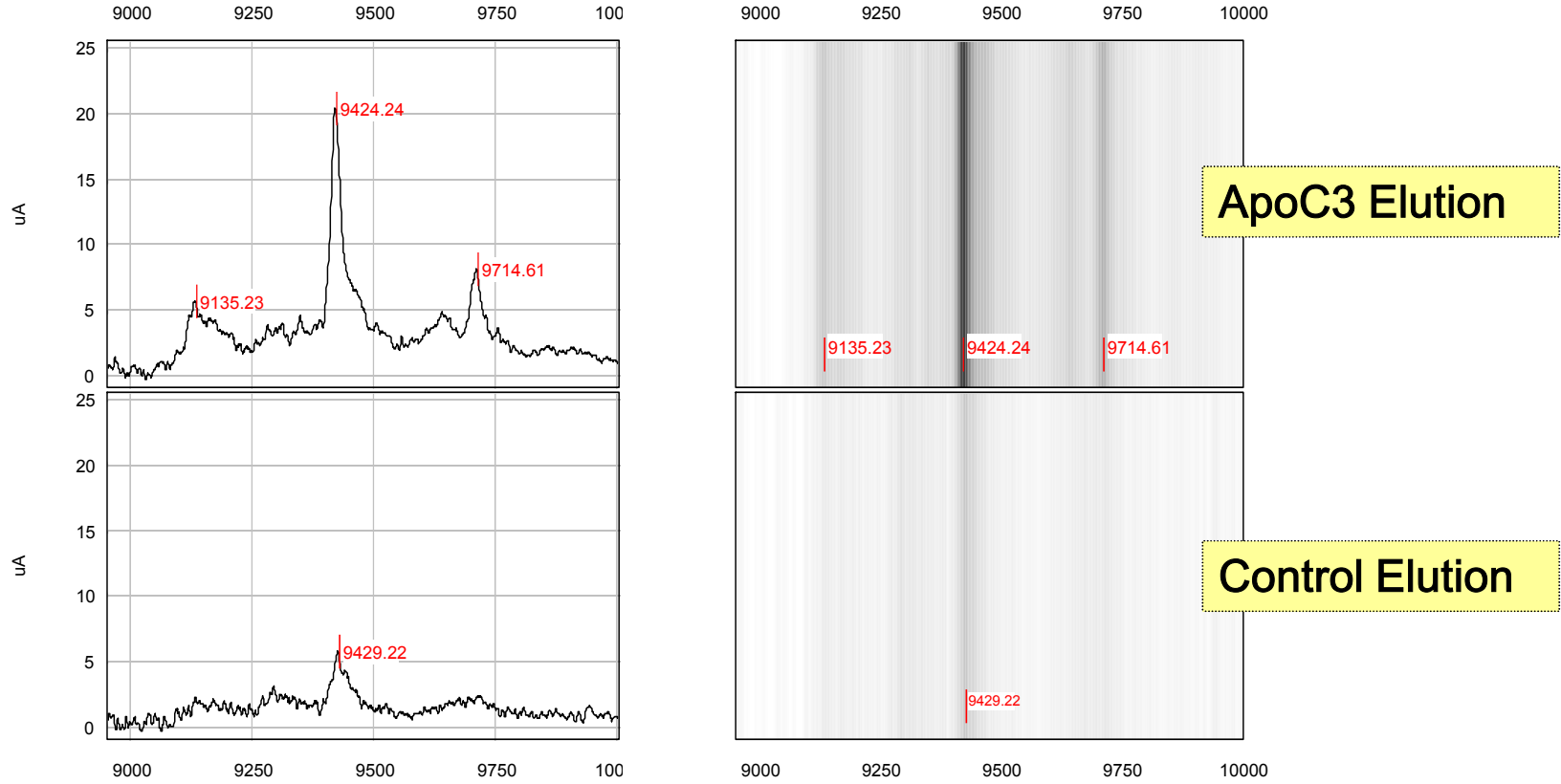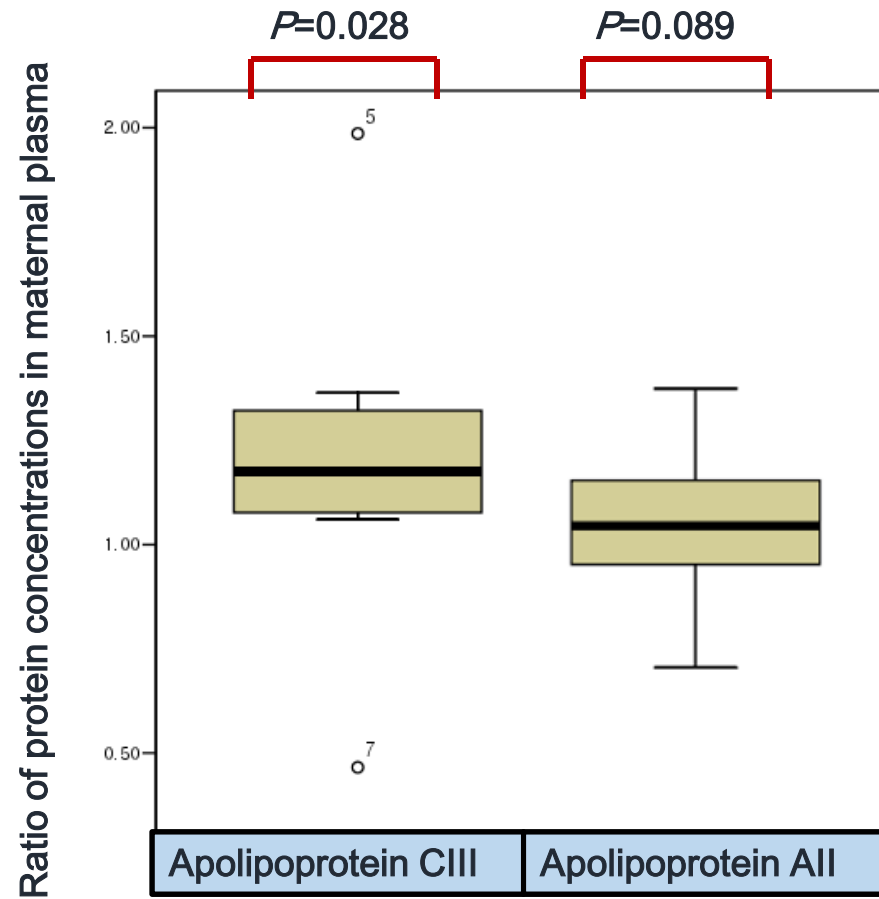
Summury

- In this study, we used proteomic profiling to identify the proteins that were differentially expressed in the plasma of women who subsequently developed GDM

- Women who subsequently developed GDM had significantly higher levels of apolipoprotein C-III than controls did. Levels of apolipoprotein A-II failed to reach statistical significance

Conclusions

1. There already exist differentially expressed proteins in the maternal circulation in the early second trimester in women who subsequently develop GDM

2. The results of this study may be applied for prediction of GDM

3. Earlier prediction or diagnosis of GDM would allow for earlier intervention which has been shown to improve obstetric outcomes

Identification of Proteomic Biomarkers in Maternal Plasma in the Early Second Trimester That Predict the Subsequent Development of Gestational Diabetes

Sun Min Kim, MD[1], Joong Shin Park, MD, PhD[1],
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Jong Kwan Jun, MD, PhD[1], Chul-Woo Kim, MD, PhD[3], and
Hee Chul Syn, MD, PhD[1]

Abstract

Introduction: This study is designed to identify proteomic biomarkers that predict the subsequent development of gestational diabetes mellitus (GDM). Methods: Maternal blood was obtained prospectively from healthy pregnant women in the early second trimester (16-20 weeks). Twelve women subsequently diagnosed with GDM at 24 to 28 weeks were selected as cases; an equal number of normoglycemic women as controls. Proteomic analysis of the previously stored plasma was performed by surface-enhanced laser desorption/ionization time-of-flight (SELDI-TOF) mass spectrometry. Results: Three peaks (9122 Da, 9412 Da, and 9701 Da) that were increased in cases were characterized as isoforms of apolipoprotein CIII. Another discriminatory peak (17 105 Da) that was decreased in cases was matched to apolipoprotein AII. Enzyme-linked immunosorbent assay (ELISA) confirmed that women who subsequently developed GDM had significantly higher levels of apolipoprotein CIII than controls did. Levels of apolipoprotein AII failed to reach statistical significance. Conclusion: Our data suggest that there already exist biomarkers in the maternal circulation at 16 to 20 weeks in women who subsequently develop GDM.

Keywords

gestational diabetes, proteomics, SELDI-TOF, apolipoprotein CIII, apolipoprotein AII

Apo C-III in type 2 diabetes

A proteomic study of the apolipoproteins in LDL subclasses in patients with the metabolic syndrome and type 2 diabetes

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Apo C-III in type 2 diabetes

Proteome Science

BioMed Central

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Government's approval for the patents

- Information processing method for early diagnosis of gestational diabetes, Monitoring for gestational diabetes, Kit for diagnosis and screening

- Early diagnostic method of gestational diabetes, apolipoprotein C3 as a biomarker for the diagnosis of gestational diabetes, apolipoprotein C3 for the diagnosis of gestational diabetes and how to use it as a biomarker

Thank you for your attention

- In all cases of GDM, pregestational diabetes mellitus was excluded using a postpartum 75-g OGTT performed at the 6 week postpartum visit
- We analyzed the levels of HbA1c in the same stored plasma at the early second trimester by SELDI-TOF. There was no difference between the cases and controls

GDM Screening in SNUH

- 50g oral glucose challenge test (GCT) in all pregnant women at 24-28 weeks of gestation

- GDM is confirmed by 100gOGTT (Carpenter-Coustan criteria) for women meeting the threshold value in the GCT

- In high risk pregnancy, the GCT is performed at the first visit. If the result is normal, the GCT is repeated at 24-28 weeks of gestation

  severe obesity, strong family history of type 2 DM, previous history of GDM, glucosuria

- Family Hx of diabetes
- Hx of adverse perinatal outcome (macrosomia, malformation, polyhydramnios, stillbirth or missed abortion)
- Maternal age > 35 years
- Obesity
- Hypertension or glycosuria

Insulin

- Long acting
- Intermediate acting
- Rapid acting (short acting)
- Very-rapid acting

Problems of the current criteria

- None of the currently recommended Dx criteria are based on pregnancy outcome.

- The differing glucose challengers and Dx criteria

→ Exceedingly difficult in comparison of prevalence and pregnancy outcomes across the world.

TABLE 5

Comparison of proposed thresholds to current thresholds for 75 gram OGTT in pregnancy (ADA)

Sample time	Proposed glucose threshold, mg/dL	Current ADA recommendations
Fasting	92	95
1-h	180	180
2-h	153	155

Proposed: gestational diabetes is diagnosed if ≥1 of the thresholds is met or exceeded.[16] Current ADA recommendations: gestational diabetes is diagnosed if ≥ 2 thresholds are met or exceeded.[12]

ADA, American Diabetes Association; *OGTT*, oral glucose tolerance test.

Coustan. The HAPO study: paving the way. Am J Obstet Gynecol 2010.

The editors of the Journal and the SMFM Publication Committee are pleased to provide this summary of a debate conducted at the 31st annual meeting of the Society for Maternal–Fetal Medicine (The Pregnancy Meeting), San Francisco, CA, Feb. 7-12, 2011. One entry in this series will run every month from May through October 2011.

Gestational diabetes—Staying with old or marrying new guidelines

THE ISSUE: Gestational diabetes mellitus is associated with increased neonatal morbidities and higher cesarean delivery rates; women with gestational diabetes mellitus are at increased risk for type II diabetes mellitus later in life. The current recommendation for screening includes a glucose tolerance test either early in pregnancy and/or at 24-28 weeks' gestation followed by a diagnostic 100-g oral 3-hour glucose tolerance test with a rate of 5%. The results of a large prospective observational study (HAPO study) and 2 randomized trials lead the International Association of Diabetes in Pregnancy Study Group to recommend a 1-stage screening and diagnosis method that includes a 75-g 2-hour glucose tolerance test that will result in an 18% gestational diabetes mellitus rate. However, there is uncertainty about the clinical implications of the adoption of the latter recommendation.

Staying with old guidelines

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5% (4-7%)

Marry old and new guidelines

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Estimated to 18%

Clinical characteristics (I)

No	Age	Parity	BMI	GA at sampling	GA at 50-g OGTT	GA at delivery	Delivery mode	PE
Case 1	38	0000	21	16^{+6}	24^{+2}	39^{+5}	VD	X
Control 1	36	0010		16^{+2}	26^{+5}	40^{+4}	VD	X
Case 2	36	0000	22	17^{+1}	26^{+5}	38^{+0}	C/S	X
Control 2	36	0000	20.2	16^{+3}	26^{+0}	40^{+5}	VD	X
Case 3	37	1011	28.1	16^{+6}	24^{+6}	39^{+5}	VD	X
Control 3	39	1011	29.4	16^{+5}	24^{+4}	38^{+3}	C/S	X
Case 4	39	0000	27.2	16^{+4}	24^{+0}	37^{+6}	C/S	X
Control 4	39	0000	22.8	16^{+0}	23^{+1}	40^{+3}	VD	X
Case 5	36	2002	22.6	17^{+6}	26^{+6}	38^{+1}	C/S	X
Control 5	35	1021	24	17^{+2}	25^{+2}	41^{+2}	VD	X
Case 6	37	2022	23.2	18^{+0}	25^{+0}	37^{+3}	VD	X
Control 6	37	2032	23	18^{+0}	24^{+1}	37^{+5}	C/S	X
Case 7	38	0020	21.6	16^{+4}	24^{+3}	39^{+0}	C/S	X
Control 7	38	0000	20.2	16^{+0}	23^{+6}	40^{+0}	VD	X
Case 8	37	2012	26.8	16^{+6}	23^{+6}	38^{+3}	C/S	X
Control 8	36	1001	22.1	16^{+1}	25^{+6}	39^{+2}	VD	X
Case 9	37	0000	19.4	17^{+6}	27^{+4}	38^{+2}	C/S	X
Control 9	38	0000	20.8	18^{+0}	25^{+0}	41^{+0}	VD	X
Case 10	29	0000	20.1	19^{+6}	28^{+3}	38^{+5}	VD	X
Control 10	31	0000		20^{+1}	26^{+1}	39^{+5}	VD	X
Case 11	38	0000	33	17^{+5}	24^{+0}	38^{+5}	VD	X
Control 11	38	0000	26.3	16^{+6}	23^{+6}	41^{+3}	C/S	X
Case 12	35	1001	22.2	16^{+6}	24^{+3}	38^{+5}	VD	X
Control 12	36	1001	19.1	16^{+5}	25^{+3}	39^{+0}	C/S	X

Clinical characteristics (II)

No	50-g OGTT	100-g OGTT	HbA1c	Insulin	Postpartum 75-g OGTT
Case 1	197	73-205-172-105	5.2	N	Impaired glucose tolerance
Control 1	164			-	-
Case 2	133	75-185-168-147	5.5	N	Impaired glucose tolerance
Control 2	147			-	-
Case 3	159	78-186-162-120	5.2	N	Follow up loss
Control 3	76			-	-
Case 4	188	98-203-219-168	6.0	Y	Follow up loss
Control 4	162			-	-
Case 5	191	85-167-172-170	5.5	Y	Normal
Control 5	115			-	-
Case 6	149	88-223-160-137	5.7	N	Follow up loss
Control 6	101			-	-
Case 7	192	87-188-194-146	5.6	N	Impaired glucose tolerance
Control 7	151	74-166-138-113		-	-
Case 8	232	115-252-177-172	6.3	Y	Follow up loss
Control 8	117			-	-
Case 9	236	82-187-173-165	5.3	N	FBS 99
Control 9	61			-	-
Case 10	157	83-217-185-156	5.3	Y	Normal
Control 10	88			-	-
Case 11		106-177-153-126	5.7	Y	Normal
Control 11	139			-	-
Case 12	148	48-227-181-89	5.5	N	Normal
Control 12	104			-	-