the new consensus criteria: two year experience in a single institution in Japan. Endocr J. 2014;61:353-8.

- Migita O, Maehara K, Kamura H, Miyakoshi K, Tanaka M, Morokuma S, et al. Compilation of copy number variants identified in phenotypically normal and parous Japanese women. J Human Genetics. 2014;59:326-31.

2. 学会発表

- 宮越敬, 正木繭, 門平育子, 福武麻里絵, 池ノ上学, 春日義史, 他. 妊娠糖尿病合併妊婦の産後早期糖代謝異常の予測因子に関する検討. 第50回日本周産期新生児医学会総会・学術集会. 2014年.
- Miyakoshi K. Clinical features of gestational diabetes mellitus by the new consensus criteria: three year experience in a single institution in Japan. 46th International Congress on Pathophysiology of pregnancy. Tokyo. 2014. 9.
- Miyakoshi K, Saisho Y, Fukutake M, Ochiai D, Matsumoto T, Minegishi K, et al. Antepartum clinical features associated with early postpartum clucose intolerance in gestational diabetes mellitus by the new criteria. 46th International Congress on Pathophysiology of pregnancy. Tokyo. 2014. 9.
- 宮越敬, 税所芳史, 福武麻里絵, 春日義史, 落合大吾, 松本直, 他. 妊娠糖尿病におけるインスリン導入リスク因子に関する検討. 第30回日本糖尿病妊娠学会年次学術集会. 2014年.
- 伊藤新, 税所芳史, 宮越敬, 福武麻里絵, 春日義史, 落合大吾, et al. 胎児肺成熟を目的としたベタメタゾン投与後の母体血糖管理に要したインスリン投与量に関する後方視的検討. 第30回日本糖尿病妊娠学会年次学術集会. 2014年.

H. 知的財産権の出願・登録状況（予定を含む。）

1. 特許取得
   本年度はなし
2. 実用新案登録
   本年度はなし
3. その他
   本年度はなし

表 1　遺伝子解析を行った遺伝子一覧

- ADAMTS9
- ADIPOQ
- ADRB3
- ANK1
- ANKRD55
- AP3S2
- ARAP1
- ARL15
- BCL11A
- BCAR1
- CILP2
- C2CD4A
- C2CD4A, C2CD4B
- CDC123, CAMK1D
- CDKAL1
- CDKN2A, CDKN2B
- CHCHD9
- DUSP9
- DGKB
- FAF1
- FTO
- GCC1
- GCK
- GCKR
- GIPR
- GLIS3
- GPSM1
- GRB14
- HHEX
- HMG20A
- HMGA2
- HNF1B
- HNF4A
- IGF2BP2
- IRS1
- ITGB6-RBMS1
- JAZF1
- KCNJ11
- KCNK17
- KCNQ1
- KLF14
- KLHDC5
- MAEA
- MC4R
- MIR129-LEP
- MPHOSPH9
- MTNR1B
- NOTCH2
- PEPD
- PPARG
- PTPRD
- PRC1
- PROX1
- PSMD6
- PTPRD
- RBM43, RND3
- RBMS1
- SLC30A8
- SPRY2
- SRR
- SSR1-RREB1
- ST6GAL1
- TCF7L2
- THADA
- TLE1
- TLE4
- TMEM154
- TP53INP1
- TSPAN8, LGR5
- UBE2E2
- VPS26A
- WFS1
- ZBED3
- ZFAND3
- ZFAND6
- ZMIZ1

表２　正常耐糖能群および妊娠糖尿病の母体背景

		正常耐糖能 (N=328)	妊娠糖尿病 (N=193)
年齢	(歳)	35.5±5.3	36.2±5.9
妊娠前 BMI	(kg/m^2)	20.5±5.0	21.6±4.4#
肥満 (BMI≧ 25)	(%)	5.2	15#
分娩週数	(週)	38.5±3.3	37.9±4.5#
児体重	(g)	2984±471	2847±599#

数値：平均±標準偏差もしくは%

#: P < 0.01

表 3　妊娠糖尿病との関連を示した遺伝子

Case-control 関連解析

Near by Gene	*P*	オッズ比
DUSP9	0.003	1.52
MTNR1B	0.004	1.48
ANKRD55	0.005	1.44
HHEX/IDE	0.024	1.49
CILP2	0.039	1.56
FTO	0.044	1.61
SPRY2	0.044	1.31

ロジスティック回帰分析

Near by Gene	*P*	オッズ比
ANKRD55	0.0004	2.15
MTNR1B	0.003	1.82
MAEA	0.007	1.68
DUSP9	0.011	1.64
HHEX/IDE	0.035	1.52
MAEA	0.036	1.49
IGF2BP2	0.036	1.51
SRR	0.040	1.48
CILP2	0.048	1.60

表 4 遺伝因子の作用および妊娠糖尿病および２型糖尿病発症との関連

Near by Gene	*インスリン作用との関連*	GDM 関連遺伝子としての報告	日本人２型糖尿病関連遺伝子としての報告
DUSP9	*インスリン感受性*	なし	あり
MTNR1B	*インスリン分泌*	あり	なし
ANKRD55	*インスリン感受性*	なし	なし
HHEX/IDE	*インスリン分泌*	あり	あり
CILP2	*インスリン感受性*	なし	あり
FTO	*インスリン感受性*	あり	あり
SPRY2	*インスリン感受性*	なし	あり
MAEA	*インスリン感受性*	なし	あり
IGF2BP2	*インスリン感受性*	あり	あり
SRR	*インスリン分泌*	あり	あり

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル	発表雑誌名	巻号	ページ	出版年
Hiroshi Yamashita, Ichiro Yasuhi, Masashi Fukuda, Yukari Kugishima, Yuki Yamauchi, Akiko Kuzume, Takashi Hashimoto, So Sugimi, Yasushi Umezaki, Sachie Suga, Nobuko Kusuda,	The association between maternal insulin resistance in mid-pregnancy and neonatal birthweight in uncomplicated pregnancies	Endocrine Journal	61(10)	1019-1024	2014
Takashi Sugiyama, Hirohito Metoki, Hirotaka Hamada, Hidekazu Nishigori, Masatoshi Saito, Nobuo Yaegashi, Hideto Kusaka, Reo Kawano, Kiyoshi Ichihara, Ichiro Yasuhi, Yuji Hiramatsu, Norimasa Sagawa, The Japan Gestational Diabetes Study Group	A retrospective multi-institutional study of treatment for mild gestational diabetes in Japan	Diabetes Research and Clinical Practice	103(3)	412-418	2014
Yukari KUGISHIMA, Ichiro YASUHI, Hiroshi YAMASHITA, Masashi FUKUDA, Akiko KUZUME, So SUGIMI, Yasushi UMEZAKI, Sachie SUGA, Nobuko KUSUDA	Risk factors associated with abnormal glucose tolerance in the early postpartum period among Japanese women with gestational diabetes.	Int J Gynaecol Obstet.	Epub ahead of print		2014
Sachie Suga, Ichiro Yasuhi, Mikihiro Aoki, Makoto Nomiyama, Norio Kubo, Kosuke Kawakami, Naohumi Okura, Kaoru Okazaki, Akira Ota & Kou Kawada	Risk factors associated with respiratory disorders in late preterm infants	The Journal of Maternal-Fetal & Neonatal Medicine	Early Online: 1-5 DOI:10.3109/14767058.2014.1003804		2014
Ikenoue S, Miyakoshi K, Saisho Y, Sakai K, Kasuga Y, Fukutake M, et al.	Clinical impact of women with gestational diabetes mellitus by the new consensus criteria: two year experience in a single institution in Japan.	Endocr J.	61	353-358	2014

発表者氏名	論文タイトル	発表雑誌名	巻号	ページ	出版年
Migita O, Maehara K, Kamura H, Miyakoshi K, Tanaka M, Morokuma S, et al.	Compilation of copy number variants identified in phenotypically normal and parous Japanese women.	J Human Genetics.	59	326-331	2014
Sugiyama T, Saito M, Nishigori H, Nagase S, Yaegashi N, Sagawa N, Waguri M, et al.	Comparison of pregnancy outcomes between women with gestational diabetes and overt diabetes first diagnosed in pregnancy: a retrospective multi-institutional study in Japan.	Diabetes Res Clin Pract.	103	20-25	2014
Sugiyama T, Nagao K, Metoki H, Nishigori H, Saito M, Tokunaga H, Nagase S, Sugawara J, Watanabe Y, Yaegashi N, Sagawa N, Sanaka M, Akazawa S, Anazawa S, Waguri M, Sameshima H, Hiramatsu Y, Toyoda N; Japan Diabetes and Pregnancy Study Group	Pregnancy outcomes of gestational diabetes mellitus according to pre-gestational BMI in a retrospective multi-institutional study in Japan.	Endocrine journal	61(4)	373-380	2014
Sato T, Sugiyama T, Kurakata M, Saito M, Sugawara J, Yaegashi N, Sagawa N, Sanaka M, Akazawa S, Anazawa S, Waguri M, Sameshima H, Hiramatsu Y, Toyoda N; Japan Diabetes and Pregnancy Study Group	Pregnancy outcomes in women with type 1 and type 2 diabetes mellitus in a retrospective multi-institutional study in Japan.	Endocrine journal	61(8)	759-764	2014
Mito, Arata, Sakamoto, Miyakoshi, Waguri, Osamura, Kugishima, Metoki, Yasuhi	Present status of clinical care for postpartum patients with hypertensive disorders of pregnancy in Japan: findings from a nationwide questionnaire survey.	Hypertension in pregnancy	in press		2015
Kato F, Hamajima T, Hasegawa T, Amano N, Horikawa R, Nishimura G, Nakashima S, Fuke T, Sano S, Fukami M, Ogata T.	IMAGe syndrome: clinical and genetic implications based on investigations in three Japanese patients.	Clin Endocrinol	80(5)	706-713	2014

発表者氏名	論文タイトル	発表雑誌名	巻号	ページ	出版年
Kappelgaard AM, Kiyomi F, Horikawa R, Yokoya S, Tanaka T.	The impact of long-term growth hormone treatment on metabolic parameters in Japanese patients with short stature born small for gestational age.	Horm Res Paediatr	81(4)	272-279	2014
Yoshizawa-Ogasawara A, Katsumata N, Horikawa R, Satoh M, Urakami T, Tanaka T.	Third-generation Aromatse Inhibitor improved Adult Height in a Japanese Boy with Testotoxicosis.	Clin Pediatr Endocrino l	23(2)	53-58	2014
Takenouchi T, Tsukahara Y, Horikawa R, Kosaki K, Kosaki R.	Four-Decade-Old Mummified Umbilical Tissue Making Retrospective Molecular Diagnosis of Ornithine Carbamoyltransferase Deficiency.	American Journal of Medecal Geneics partA	164A(10)	2679-2681	2014
Izumi Y, Musha I, Suzuki E, Iso M, Jinnno T, Horikawa R, Amemiya S, Ogata T, Fukami M, Ohtake A.	Hypogonadotropic hypogonadism in a female patient previously diagnosed as having waardernburg syndrome due to a sox10 mutation.	Endocrine	Epub ahead of print		2014
Izumi Y, Suzuki E, Kanzaki S, Yatsuga S, Kinjo S, Igarasi M, Maruyama T, Sano S, Horikawa R, Sato N, Nakabayashi K, Hata K, Umezawa A, Ogata T, Yoshimura Y, Fukami M.	Genome-wide copu number analysis and systematic mutataion screening in 58 patients with hypogonadotropic hypogonadism.	Fertil Steril	102(4)	1130-1136	2014
Hori T, Yamaguchi S, Shinkaku H, Horikawa R, Shigematsu Y, Takayanagi M, Fukao T.	Inborn errors of ketone body utilization.	Pediatr Int	Epub ahead of print		2015
Chida N, Kobayashi I, Takezaki S, Ueki M, Yamazaki Y, Garelli S, Scarpa R, Horikawa R, Yamada M, Betterle C, Notarangelo LD, Yawaka Y, Ariga T.	Disease specificity of anti-tryptophan hydroxylase-1 and anti-AIE-75 autoantibodies in APECED and IPEX syndrome.	Clin Immunol	156(1)	36-42	2015

発表者氏名	論文タイトル	発表雑誌名	巻号	ページ	出版年
安日一郎	血糖自己測定法（SMBG）とリスク因子を用いた妊娠糖尿病への戦略的アプローチ	糖尿病と妊娠	14(1)	10-15	2014
釘島ゆかり、山下洋、三好康広、藤田愛、渡邉剛志、水谷佳敬、楠目晃子、杉見創、梅崎靖、菅幸恵、福田雅史、楠田展子、安日一郎	妊娠糖尿病の新診断基準例の産褥早期予後とそのリスク因子	糖尿病と妊娠	14(1)	105-109	2014
水谷佳敬、山下洋、三好康広、藤田愛、渡邉剛志、楠目晃子、杉見創、梅崎靖、菅幸恵、釘島ゆかり、福田雅史、楠田展子、安日一郎	血糖コントロール良好な1型糖尿病合併妊娠にネフローゼ症候群を続発した１例	糖尿病と妊娠	14(1)	130-134	2014
邸冬梅，坂本なほ子，荒田尚子，大矢幸弘	低出生体重児の母体要因に関する疫学研究	厚生の指標	61(1)	1-8	2014
宮越敬，安日一郎，釘島ゆかり，三戸麻子，和栗雅子，坂本なほ子，長村杏奈，荒田尚子	分娩分娩取り扱い施設を対象とした妊娠糖尿病診療に関するアンケート調査報告	糖尿病と妊娠	14 (1)	83-87	2014
荒田尚子，和栗雅子，安日一郎，宮越敬，釘島ゆかり，長村杏奈，三戸麻子，坂本なほ子	妊娠糖尿病を合併した女性のフォローアップに関する医療者および医療機関への実態調査 - 我が国における糖尿病専門医および周産期医療施設内科医を対象としたアンケート調査 -	糖尿病と妊娠	14 (1)	88-92	2014
和栗雅子	耐糖能異常患者のプレ妊娠からの療養指導	糖尿病と妊娠	14 (1)	60-66	2014
和栗雅子	糖尿病・GDMの病態生理	臨床助産ケア	9・10月号	39-42	2014
和栗雅子	GDMのリスクと重症化予防	臨床助産ケア	11-12月号	82-87	2014
和栗雅子	糖尿病・妊娠糖尿病	調剤と情報	20(11)	54-58	2014
葛谷実和，和栗雅子，小森綾乃，山田佑子，別所恵，和田芳直，光田信明，中西　功	胃亜全摘術後、後期ダンピング症候群を伴う妊婦の血糖管理にCGMが有効であった1例	糖尿病と妊娠	14 (1)	120-125	2014

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版年	ページ
安日一郎	糖尿病妊婦	荒木栄一，山田佑一郎	ヴィジュアル　糖尿病のすべて：糖尿病患者の食事と運動：考え方と進め方	中山書店	2014	107-113
和栗雅子	妊婦の糖尿病	監修：山口徹・北原光夫総編集：福井次矢・高木　誠・小室一成	今日の治療指針	医学書院	2014	680-681
荒田尚子	食事療法の実際　糖尿病合併妊娠と妊娠糖尿病	日本糖尿病学会	糖尿病専門医研修ガイドブック　改訂第６版	診断と治療社	2014	181-182
堀川玲子	低血糖・代謝異常を疑う子どもの観察と評価	及川郁子監修　西海真理・伊藤龍子責任編集	小児看護ベストプラクティス	中山書店	2014	86-87
堀川玲子	さまざまな症状や検査異常への対応と診断、治療　非典型的外性器（外性器異常）	有阪治編集	ビギナーのための小児内分泌診療ガイド	中山書店	2014	140-149

Ⅳ. 研究成果の刊行物・別刷

Endocrine Journal 2014, **61** (10), 1019-1024

ORIGINAL

The association between maternal insulin resistance in mid-pregnancy and neonatal birthweight in uncomplicated pregnancies

Hiroshi Yamashita, Ichiro Yasuhi, Masashi Fukuda, Yukari Kugishima, Yuki Yamauchi, Akiko Kuzume, Takashi Hashimoto, So Sugimi, Yasushi Umezaki, Sachie Suga and Nobuko Kusuda

Department of Obstetrics and Gynecology, NHO Nagasaki Medical Center, Omura 856-8562, Japan

Abstract. There have been few studies performed to address the association between the degree of physiological increase in maternal insulin resistance during pregnancy and neonatal birthweight in non-diabetic pregnancy. We attempted to determine whether maternal insulin resistance, as measured by homeostasis model assessment-insulin resistance (HOMA-IR), in mid-pregnancy is associated with neonatal birthweight in normal pregnancies. In this retrospective observational study, we measured HOMA-IR in singleton healthy pregnant women who underwent a 75 g oral glucose tolerance test (OGTT) in mid-pregnancy because of a positive diabetes screen. Using multivariate analyses to adjust for maternal parity, pre-gestational obesity, gestational weight gain, plasma glucose levels, and gestational age at delivery, we tested the association between HOMA-IR and birthweight in their offspring. We also tested the association HOMA-IR and a risk of large-for-gestational-age (LGA) infants. In 655 Japanese women, HOMA-IR was positively associated with birthweight after adjusting for these confounders ($p<0.05$). A higher HOMA-IR was significantly associated with an increased incidence of LGA infants with an adjusted odds ratio of 1.53 (95% confidence interval, 1.10-2.15) per 1 unit of HOMA-IR. The degree of maternal insulin resistance in mid-pregnancy was associated with birthweight and the risk of giving birth to an LGA infant in normal pregnancies, independent of maternal obesity and glucose levels.

Key words: Insulin resistance, HOMA-IR, Pregnancy, Birthweight, Macrosomia

IN COMPARISON with the non-pregnant state, the postprandial glucose concentration is elevated in pregnant subjects, especially during late pregnancy [1]. Postprandial maternal hyperglycemia is thought to accelerate glucose transfer from mother to fetus, which guarantees normal fetal growth during pregnancy. An increase in maternal insulin resistance during pregnancy manifests in early gestation [2], and causes physiological maternal postprandial hyperglycemia. Accordingly, the degree of maternal insulin resistance manifested during pregnancy is theoretically associated with the degree of glucose flux from mother to fetus. Gestational diabetes mellitus (GDM) is a typical example. Accompanied with beta cell dysfunction, excessive manifestation of insulin resistance during pregnancy is associated with the development of GDM [3]. In women with GDM, it is thought that maternal hyperglycemia leads to fetal hyperglycemia and hyperinsulinemia, which cause fetal macrosomia. Excessive insulin resistance during pregnancy is also observed in obese subjects without abnormal glucose tolerance [4], and fetal macrosomia is also common in these patients.

However, to the best of our knowledge, there have been few studies performed to address the association between the degree of physiological increase in maternal insulin resistance during pregnancy and neonatal birthweight in non-diabetic pregnancy. The aim of this study was to determine whether elevated maternal insulin resistance, as measured by the homeostasis model assessment-insulin resistance (HOMA-IR) in the second and third trimesters, is associated with increased neonatal birthweight, and therefore a risk of

Submitted Apr. 11, 2014; Accepted Jul. 10, 2014 as EJ14-0163
Released online in J-STAGE as advance publication Aug. 8, 2014

Correspondence to: Ichiro Yasuhi, M.D., Department of Obstetrics and Gynecology, NHO Nagasaki Medical Center, 1001-1 2-chome Kubara, Omura City, Nagasaki 856-8562, Japan.
E-mail: yasuhi@nagasaki-mc.com

macrosomic infants after controlling for maternal obesity and plasma glucose (PG) levels in uncomplicated healthy pregnancies.

Material and Methods

This was a retrospective study using our GDM screening database over a six-year period from 2004 to 2009 at the Nagasaki Medical Center. This study was approved by the Institutional Review Board of Nagasaki Medical Center with written informed consent obtained from all subjects. All pregnant subjects were screened for GDM between the second and third trimesters using a 50 g glucose challenge test (GCT). In subjects with a positive GCT (≥ 135 mg/dL), we performed a 75 g oral glucose tolerance test (OGTT) after an overnight fast. Among the subjects who underwent OGTT during the trimesters, we included only those with healthy singleton pregnancies with normal OGTT results as determined by Japan Society of Obstetrics and Gynecology (JSOG) criteria [5]. We defined a normal OGTT test result as all three normal values of <100 mg/dL at fasting, <180 mg/dL at 1-hour, and <150 mg/dL at 2-hour after a 75 g oral glucose loading. We did not apply the new diagnostic criteria, *i.e.* the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [6] during the study period, because it was not adopted by the JSOG until June, 2010. At the time of OGTT, we also measured serum immunoreactive insulin (IRI) concentrations at fasting. We used HOMA-IR as a surrogate index of maternal insulin resistance, which was calculated by the equation {[fasting PG level](mg/dL) × [fasting IRI level](μU/mL)/405}. We defined large-for-gestational age (LGA) infants by using the 90th percentile of the standard Japanese infantile growth curve [7].

We excluded patients with GDM in order to avoid treatment bias, as we treated the patients with the aim of preventing perinatal complications associated with GDM, including neonatal macrosomia. We also excluded women with hypertensive disorders, other maternal medical complications, including systemic lupus erythematosus and thyroid disease, and those with fetal malformation. In the remaining patients, we examined the association between the neonatal birthweight and predictive variables, including maternal PG and HOMA-IR at OGTT, parity, pre-pregnancy body mass index (BMI), and weight gain during pregnancy by using univariate regression analysis after adjusting for gestational age (GA) at delivery. Then we tested the association between the maternal HOMA-IR and neonatal birthweight by multivariate regression analysis to adjust for confounding variables, including parity, pre-pregnancy BMI, weight gain during pregnancy, glucose values at OGTT, and GA at delivery. We also examined the association between maternal HOMA-IR and risk for LGA infants by using multiple logistic regression models after adjusting for these confounders. A p-value < 0.05 was considered to be significant.

Results

The maternal characteristics, results of 75 g OGTT, and neonatal outcomes of the 655 Japanese women involved in this study are summarized in Table 1. Mean GA at the time of OGTT was 28.3±6.3 weeks of gestation, and 224 (34%) and 431 (66%) subjects had the 75 g OGTT in their second and third trimester, respectively. Mean HOMA-IR among all subjects was 1.4±0.8. Since the mean HOMA-IR values were 1.34±0.92 and 1.46±0.79 in the second and third trimesters, respectively, and these were not significantly different (p=0.38), we combined the data together for the analysis.

In the univariate analysis after adjusting for GA at delivery, parity (multipara *vs.* primipara, r^2=0.35, p=0.001), pre-pregnancy BMI (r^2=0.36, p<0.001), weight gain during pregnancy (r^2=0.37, p<0.001),

Table 1 Maternal characteristics, results of the 75 g OGTT, and neonatal outcomes (n=655)

	Mean±SD or N (%)
Age (y/o)	31.9±4.9
Primipara (%)	307 (46.9)
Pre-pregnancy BMI (kg/m^2)	22.0±4.0
Weight gain during pregnancy (kg)	9.7±4.1
GA at 75 g OGTT (wk)	28.3±6.3
Fasting PG (mg/dL)	79.5±6.5
1h-PG (mg/dL)	144.1±25.0
2h-PG (mg/dL)	122.8±22.7
Fasting IRI (μU/mL)	7.1±3.8
HbA1c (%) (mmol/mol)	5.3±0.5 (34.0±3.1)
HOMA-IR	1.4±0.8
GA at delivery (wk)	39.1±1.7
Birth weight (g)	3,039±466
LGA infants (%)	91 (13.9%)

BMI, body mass index; GA, gestational age; PG, plasma glucose; IRI, immunoreactive insulin; HOMA-IR, homeostasis model assessment-insulin resistance; LGA, large-for-gestational age.

Table 2 Adjusted odds ratios of HOMA-IR for giving birth to a large-for-gestational age infant in the multivariate logistic regression models

Predictive variables	Model I adjusted for FPG		Model II adjusted for 1-hour PG		Model III adjusted for 2-hour PG		Model IV adjusted for all PG	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
HOMA-IR	1.55 (1.11-2.17)	0.0099	1.49 (1.11-2.00)	0.008	1.46 (1.09-1.95)	0.012	1.53 (1.10-2.15)	0.012
Pre-pregnancy BMI (kg/m^2)	1.08 (1.00-1.16)	0.044	1.08 (1.00-1.16)	0.044	1.08 (1.00-1.15)	0.042	1.12 (1.00-1.16)	0.041
Weight gain during pregnancy (kg)	1.11 (1.05-1.18)	0.0003	1.11 (1.05-1.18)	0.0003	1.12 (1.05-1.18)	0.0002	1.19 (1.06-1.19)	0.0001

OR, odds ratio; CI, confidence interval; BMI, body mass index; GA, gestational age; FPG, fasting plasma glucose; PG, plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance.

fasting PG (r^2=0.35, p<0.001), 1-hour PG (r^2=0.34, p <0.001), 2-hour PG (r^2=0.34, p<0.001), and HOMA-IR (r^2=0.36, p<0.001) were significantly associated with neonatal birthweight. We examined the association between HOMA-IR and neonatal birthweight using multivariate regression analysis adjusting for these confounders including GA at delivery, parity, pre-pregnancy BMI, weight gain during pregnancy, fasting PG, 1-hour PG, and 2-hour PG levels. Maternal HOMA-IR was significantly and positively associated with neonatal birthweight after adjusting for these confounders (p<0.05). In this multivariate regression model, the parity (p<0.001), the pre-pregnancy BMI (p<0.0001), and the weight gain during pregnancy (p<0.001) were also independent variables associated with neonatal birthweight. On the other hand, we did not find any association between maternal PG levels and neonatal birthweight.

Ninety-one women (13.9%) had an LGA infant (Table 1). We examined multivariate logistic models regarding the risk of delivery of an LGA infant (Table 2), in which the GA at delivery, parity, pre-pregnancy BMI, weight gain during pregnancy, and each PG (in models I to III) and all PG (in model IV) were controlled as confounders. In each model, HOMA-IR was a significant independent risk factor of giving birth to an LGA infant after controlling for the confounders. For example, in model IV, HOMA-IR was an independent risk factor of giving birth to an LGA infant with an adjusted odds ratio (OR) of 1.53 (95% confidence interval [CI], 1.10-2.15; p=0.012) per 1 unit of HOMA-IR. In each model, the pre-pregnancy BMI and the gestational weight gain remained significantly associated with giving birth to an LGA infant (Table 2). However, neither the parity nor the PG levels were associated with LGA infants in the models.

Discussions

In healthy non-diabetic singleton pregnancies, we found that the maternal HOMA-IR in the second and third trimesters was significantly and positively associated with the neonatal birthweight after adjusting for the parity, pre-pregnancy BMI, weight gain during pregnancy, and PG levels. Elevated maternal HOMA-IR was an independent risk factor of giving birth to an LGA infant after controlling for these confounding variables. To the best of our knowledge, this is the first report to demonstrate a significant association between maternal HOMA-IR and fetal growth independent of maternal obesity and PG levels in normal pregnancy.

In previous studies, investigators did not find any independent association between maternal insulin resistance during pregnancy and neonatal birthweight in subjects with or without GDM. Voldner *et al.* [8] investigated the relationship between fetal macrosomia and maternal metabolic measures, including their fasting PG, fasting insulin, and HOMA-IR at 30-32 weeks of gestation in 553 non-GDM Caucasian females. They found that only the fasting PG, and neither the fasting insulin nor HOMA-IR, was associated with macrosomia after adjusting for covariates including maternal BMI. Bomba-Opon *et al.* [9] examined the association between maternal HOMA-IR in the third trimester and neonatal birthweight in 121 patients with GDM, and could not find any association. Das *et al.* found a significant association between maternal HOMA-IR and ultrasonographically-determined fetal growth at 24-28 weeks of gestation in 86 women with normal glucose tolerance [10]. Although they adjusted for maternal PG levels, they did not control for maternal obesity and did not address neonatal birthweight. The Japanese pop-

ulation is the least obese among developed countries [11], and in this study the subjects had a mean standard pre-pregnancy BMI of 22.0 kg/m^2. It is possible that the difference in basic obesity between Japanese and other ethnic populations may contribute to a difference between our study and other studies. Maternal BMI is strongly associated with neonatal birthweight independent of maternal glucose levels [12], and obesity is also significantly associated with insulin resistance. Therefore, to determine whether maternal insulin resistance is associated with fetal growth independent of maternal obesity in the obese population rather than less obese population like Japanese subjects, much more sample size would be necessary.

We combined the HOMA-IR data from the second and third trimesters, because there were no significant differences between them. Maternal insulin resistance is already increased in early gestation in comparison with the pre-pregnant state in healthy pregnant subjects [2]. Although the change in insulin resistance between the second and third trimesters has not been well documented in normal pregnancy, some authors have reported that no significant change was observed in the maternal HOMA-IR between the trimesters in either non-obese or obese women with normal glucose tolerance [13]. Cohen *et al.* reported that the HOMA-IR is appropriate for use during the second and third trimesters of pregnancy even in obese patients [14].

In terms of the association between maternal hyperglycemia and neonatal birthweight, Voldner *et al.* [8] reported that the maternal fasting PG was the only independent risk factor associated with neonatal macrosomia. A large multicenter prospective observational study called the HAPO study [15] confirmed that each maternal PG level during 75 g OGTT in mid-pregnancy was independently associated with giving birth to an LGA neonate, and that the fasting PG showed the strongest association. In the HAPO study, however, they did not address maternal insulin status. In the univariate analyses in our study, we also found that each PG during 75 g OGTT was significantly associated with neonatal birthweight, and that the fasting PG was the strongest. However, the association was no longer significant in the multivariate regression models including HOMA-IR and the pre-pregnancy BMI as covariates. While the association between maternal PG levels and neonatal birthweight cannot be independent from maternal HOMA-IR, since there is a link between maternal PG levels and insulin resistance in normal pregnancy, HOMA-IR in mid-pregnancy could well be a better predictive variable for neonatal birthweight and macrosomia than maternal PG levels because of its lack of reproducibility during OGTT in uncomplicated pregnancies. Again, the lack of statistical power may have affected the identification of such a modest association in non-diabetic healthy pregnant subjects in a previous study [8].

It is well-documented that maternal pre-pregnancy BMI and excessive gestational weight gain are independently associated with fetal macrosomia in non-diabetic pregnancy [16-18]. A subanalysis of the HAPO study showed that maternal obesity was significantly associated with macrosomia, independent of maternal PG levels [19]. In our study, we found that maternal pre-pregnancy BMI and gestational weight gain were individually associated with having an LGA infant, independent of not only maternal glycemic levels, but also insulin resistance status. Although maternal obesity, excessive gestational weight gain and insulin resistance during pregnancy are interrelated [20, 21], our results showed that these three factors may independently influence fetal overgrowth during normal pregnancy.

There are several limitations to this study. Firstly, we did not directly measure insulin resistance. Although the gold standard used to measure insulin resistance *in vivo* is the euglycemic glucose clamp method [22], because of the complexity of the clamp method, we were obliged to use surrogate indices of insulin resistance which are often used in the clinical setting. HOMA-IR is known to show a good linear correlation to insulin resistance directly measured by glucose clamp technique in non-pregnant adults [23-25]. Although HOMA-IR during pregnancy is less correlated to directly measured insulin resistance by clamp method in comparison with females in a non-pregnant state, it is still a significant predictor of total insulin sensitivity throughout pregnancy and may be a useful tool to assess maternal insulin status [14, 26]. Secondly, we did not measure neonatal adiposity. Neonatal adiposity is well recognized in infants born from diabetic and gestational diabetic mothers and is a very sensitive marker of abnormal fetal overgrowth [27, 28]. Walsh *et al.* [29] reported that the maternal fasting PG concentration at 24 weeks of gestation was significantly associated with both infant birthweight and adiposity in healthy non-diabetic mothers. Although further examinations are necessary, maternal HOMA-IR, a surrogate marker of insulin resistance, is expected to provide a

new predictor of neonatal adiposity in diabetic and/or non-diabetic healthy mothers.

In terms of clinical significance, we were able to use HOMA-IR levels to assess the risk of having a macrosomic infant in women without GDM. Although we did not include patients with gestational diabetes in this study due to therapeutic bias, HOMA-IR levels may also be useful to estimate the risk of macrosomia in such patients. It has been reported that the prevalence of GDM has increased since applying the new IADPSG diagnostic criteria [6], and it may be possible to make triage decisions based on HOMA-IR level in order to assess the risk of macrosomia.

In summary, maternal HOMA-IR in the second and third trimesters was significantly associated with neonatal birthweight and the risk of giving birth to an LGA infant after controlling for GA at birth, maternal parity, pre-pregnancy BMI, weight gain during pregnancy, and PG levels in uncomplicated pregnancies. Our findings suggest that the degree of insulin resistance in mid-pregnancy plays an important role in fetal growth in normal healthy pregnancies, independent of maternal obesity and glucose levels.

Disclosure

None of the authors have any potential conflict of interest to disclose associated with this research.

References

1. Freinkel N (1980) Banting lecture 1980. Of pregnancy and progeny. *Diabetes* 29: 1023-1035.
2. Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EA (1991) Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. *Am J Obstet Gynecol* 165(6 Pt 1): 1667-1672.
3. Catalano PM, Tyzbir ED, Wolfe RR, Calles J, Roman NM, et al. (1993) Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. *Am J Physiol* 264: E60-67.
4. Catalano PM, Huston L, Amini SB, Kalhan SC (1999) Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus. *Am J Obstet Gynecol* 180: 903-916.
5. Committee on Nutrition and Metabolism of the Japan Society of Obstetrics and Gynecology (1984) The committee report. *Acta Obstet Gyneacol Jpn* 36: 505-511.
6. International Association for Diabetes and Pregnancy Study Groups Consensus Panel (2010) International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 33: 676-682.
7. Itabashi K, Fujimura M, Kusuda S, Tamura M, Hayashi T, Takahashi T, et al. (2010) Introduction of new neonatal standard anthropometric measurements. *Nihon Shonika Gakkai Zasshi* 114: 1271-1293 (in Japanese).
8. Voldner N, Qvigstad E, Frøslie KF, Godang K, Henriksen T, Bollerslev J (2010) Increased risk of macrosomia among overweight women with high gestational rise in fasting glucose. *J Matern Fetal Neonatal Med* 23: 74-81.
9. Bomba-Opon DA, Wielgos M, Horosz E, Bartkowiak R, Szymusik I, et al. (2009) Maternal plasma cytokines concentrations and insulin resistance in first trimester in relation to fetal growth. *Neuro Endocrinol Lett* 30: 729-732.
10. Das S, Behera MK, Misra S, Baliarsihna AK (2010) Beta-cell function and insulin resistance in pregnancy and their relation to fetal development. *Metab Syndr Relat Disord* 8: 25-32.
11. Organisation for Economic Co-operation and Development (2010) Quality of life: Health: Obesity (2010). OECD Factbook 2010, Paris: 232-233.
12. HAPO Study Cooperative Research Group (2010) Hyperglycaemia and adverse pregnancy outcome (HAPO) study: associations with maternal body mass index. *BJOG* 17: 575-584.
13. Endo S, Maeda K, Suto M, Kaji T, Morine M, et al. (2006) Differences in insulin sensitivity in pregnant women with overweight and gestational diabetes mellitus. *Gynecol Endocrinol* 22: 343-349.
14. Cohen O, Epstein GS, Weisz B, Homko CJ, Sivan E (2006) Longitudinal assessment of insulin sensitivity in pregnancy. Validation of the homeostasis model assessment. *Clin Endocrinol (Oxf)* 64: 640-644.
15. HAPO Study Cooperative Research Group (2008) Hyperglycemia and adverse pregnancy outcomes. *N Eng J Med* 358: 1991-2002.
16. Frederick IO, Williams MA, Sales AE, Martin DP, Killien M (2008) Pre-pregnancy body mass index, gestational weight gain, and other maternal characteristics in relation to infant birth weight. *Matern Child Health J* 12: 557-567.
17. Nohr EA, Vaeth M, Baker JL, Sorensen Tla, Olsen J, Rasmussen KM (2008) Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. *Am J Clin Nutr* 87: 1750-1759.

18. Li N, Liu E, Guo J, Pan L, Li B, et al. (2013) Maternal prepregnancy body mass index and gestational weight gain on pregnancy outcomes. *PLoS One* 8: e82310.
19. HAPO Study Cooperative Research Group (2010) Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. *BJOG* 117: 575-584.
20. Catalano PM (2010) Obesity, insulin resistance, and pregnancy outcome. *Reproduction* 140: 365-371.
21. Stuebe AM, McElrath TF, Thadhani R, Ecker JL (2010) Second trimester insulin resistance, early pregnancy body mass index and gestational weight gain. *Matern Child Health J* 14: 254-60.
22. DeFronzo RA, Tobin JD, Andres R (1979) Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237: E214-223.
23. Phillips DI, Clark PM, Hales CN, Osmond C (1994) Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. *Diabet Med* 11: 286-292.
24. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, et al. (2000) Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 23: 57-63.
25. Muniyappa R, Lee S, Chen H, Quon MJ (2008) Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. *Am J Physiol Endocrinol Metab* 294: E15-26.
26. Kirwan JP, Huston-Presley L, Kalhan SC, Catalano PM (2001) Clinically useful estimates of insulin sensitivity during pregnancy: validation studies in women with normal glucose tolerance and gestational diabetes mellitus. *Diabetes Care* 24: 1602-1607.
27. Kehl RJ, Krew MA, Thomas A, Catalano PM (1996) Fetal growth and body composition in infants of women with diabetes mellitus during pregnancy. *J Matern Fetal Med* 5: 273-280.
28. Catalano PM, Thomas A, Huston-Presley L, Amini SB (2003) Increased fetal adiposity: a very sensitive marker of abnormal in utero development. *Am J Obstet Gynecol* 189: 1698-1704.
29. Walsh JM, Mahony R, Byrne J, Foley M, McAuliffe FM (2011) The association of maternal and fetal glucose homeostasis with fetal adiposity and birthweight. *Eur J Obstet Gynecol Reprod Biol* 159: 338-341.

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

A retrospective multi-institutional study of treatment for mild gestational diabetes in Japan

Takashi Sugiyama[a,1,*], *Hirohito Metoki*[a], *Hirotaka Hamada*[a], *Hidekazu Nishigori*[a], *Masatoshi Saito*[a], *Nobuo Yaegashi*[a], *Hideto Kusaka*[b,1], *Reo Kawano*[c], *Kiyoshi Ichihara*[c], *Ichiro Yasuhi*[d], *Yuji Hiramatsu*[e], *Norimasa Sagawa*[f]
The Japan Gestational Diabetes Study Group[2]

[a] *Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Sendai, Miyagi 980-8574, Japan*
[b] *Department of Obstetrics and Gynecology, National Hospital Organization Mie Chuo Medical Center, Tsu, Mie 514-1101, Japan*
[c] *Department of Laboratory Science, Faculty of Health Science, Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi 755-8505, Japan*
[d] *Department of Obstetrics and Gynecology, National Hospital Organization Nagasaki Medical Center, Omura, Nagasaki 856-8562, Japan*
[e] *Department of Obstetrics and Gynecology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan*
[f] *Department of Obstetrics and Gynecology, Rakuwakai Otowa Hospital, Kyoto 607-8062 Japan*

* *Corresponding author at*: Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai City, Miyagi 980-8574, Japan. Tel.: +81 22 717 7254; fax: +81 22 717 7258.
E-mail address: tmyka9922@gmail.com (T. Sugiyama).

[1] These authors contributed equally to this work.

[2] The contributors of the Japan Gestational Diabetes Study Group are shown as follows: *Hokkaido University* – Hisanori Minakami, Mamoru Morikawa; *Saitama Medical University* – Atsushi Itakura, Yoshinori Mizukami; *Nishisaitama-Chuo National Hospital* – Atsushi Yoshida; *Gunma University Schoo of Medicine* – Koushi Hashimoto, Aya Ohsaki; *Saiseikai Central Hospital* – Sonoko Anazawa, Kiyoshi Kamei; *Aiiku Hospital* – Masao Nakabayashi, Yoshiji Takeda; *Keio University* – Kei Miyakoshi, Satoru Ikenoue; *Shiseikai Daini Hospital* – Masashi Honda; *National Hospital Organization Nagasaki Medical Center* – Haruhiko Sago, Naoko Arata, Kohei Ogawa; *Nihon University School of Medicine* – Tatsuo Yamamoto, Masashi Nagaishi; *Tokyo Medical Center* – Jun Takahashi; *Tokyo Women's University School of Medicine* – Yoshio Matsuda, Yasuo Makino, Masaki Ogawa, Mayumi Sanaka; *Tokyo Women's University Yachiyo Medical Center* – Naoki Masaoka, Yoshiyuki Nakajima; *St. Marianna University School of Medicine* – Mamoru Tanaka, Suguru Igarashi; *Yokohama City University Medical Center* – Tsuneo Takahashi, Mika Okuda; *Ebina Hospital*: Yasue Omori, Natsuko Suzuki; *Mie University Graduate School of Medicine* – Tomoaki Ikeda, Yuki Kamimoto; *Osaka City General Hospital* – Mariko Fukumoto Masayuki Hosoi; *Nara Medical University* – Hiroshi Kobayashi, Katsuhiko Naruse; *Osaka Medical Center and Research Institute for Maternal and Children Health* – Nobuaki Mitsuda, Keisuke Ishii, Masako Waguri, Isao Nakanishi; *Okayama University School of Medicine* – Hisashi Masuyama, Etsuko Nobumoto; The Sakakibara Heart Institute of Okayama – Ikki Simizu; *National Hospital Organization Kokura Medical Center* – Naoko Suwaki; *Tokushima University School of Medicine* – Minoru Irahara, Kazutoshi Maeda; *Ehime Prefectural Central Hospital* – Emiko Abe; *Kurume Medical University* – Daizo Hori, Yutaka Kozuma; *National Hospital Organization Nagasaki Medical Center* – Ichiro Yasuhi, Hiroshi Yamashita; *Nagasaki University School of Medicine* – Eiji Kawasaki, Ai Sakanaka; *Miyazaki University School of Medicine* – Hiroshi Sameshima, Yuki Kodama; *Uenomachi Kajiya Clinic* – Masako Kajiya; *Kagoshima City Hospital* – Masato Kamitomo.

0168-8227/$ – see front matter
http://dx.doi.org/10.1016/j.diabres.2013.12.017

ARTICLE INFO

Article history:
Received 9 April 2013
Received in revised form
17 October 2013
Accepted 18 December 2013
Available online 15 January 2014

Keywords:
Gestational diabetes mellitus (GDM)
Treatment
Pregnancy outcome
LGA

ABSTRACT

Aims: To determine whether treating mild gestational diabetes mellitus (GDM) is associated with improvement of pregnancy outcomes in Japan.

Methods: In a multi-institutional retrospective study, we examined pregnant women meeting the criteria for mild GDM (i.e., only one abnormal value [OAV] for 75-g OGTT; fasting glucose ≥100 mg/dL, 1-h postprandial glucose ≥180 mg/dL, and 2-h postprandial glucose ≥150 mg/dL), receiving either routine prenatal care (non-treatment group) or dietary intervention alone or dietary intervention with self-monitoring of blood glucose and/or insulin therapy, if necessary (treatment group). Pregnancy outcomes were compared between these groups.

Results: Data from 893 eligible women were collected from 30 institutions. Participants included 542 untreated and 351 treated women. Although there were no significant differences in baseline clinical characteristics or maternal and perinatal outcomes between these groups, the incidence of large-for-gestational-age (LGA) infants was lower in the treatment group ($P = 0.07$). Multiple logistic regression analysis (MLRA) revealed that pre-pregnancy BMI and gestational weight gain were associated with LGA infants, while 75-g OGTT results were unrelated to LGA. When overweight and obese women were the subjects, the number of LGA infants was significantly lower in the intervention than in the control group, and gestational weight gain was significantly lower in the treatment than in the control group. MLRA showed that intervention was significantly related to a lower incidence of LGA infants.

Conclusions: Our study suggests that maternal BMI impacts fetal growth and that treatment for overweight or obese mothers with OAV is associated with a lower frequency of LGA infants.

1. Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that first occurs or is first identified during pregnancy [1]. New criteria for diagnosing GDM were recently proposed by the International Association of Diabetes in Pregnancy Study Group (IADPSG) [2]. Maternal hyperglycemia correlates with adverse maternal, fetal, and/or neonatal outcomes [3]. The new criteria are based primarily on glucose levels associated with a 1.75-fold increased risk of giving birth to a large-for-gestational-age (LGA) infant in the Hyperglycemia Adverse Pregnancy Outcome (HAPO) study [3]. The frequency of this condition is increasing worldwide. In fact, the new criteria will result in a GDM prevalence of 17.8% [2], doubling the numbers of pregnant women currently diagnosed. LGA infants are well known to be a significant obstetrical complication of GDM [4,5]. The neonatal complications of GDM, including hypoglycemia and hypocalcemia, are due mainly to fetal hyperinsulinemia, which results from maternal hyperglycemia. The long-term complications of GDM are type 2 diabetes development in the mother [6,7] and diabetes and/or obesity in their offspring [8,9].

In 2010, the criteria for diagnosing GDM proposed by the IADPSG were adopted in Japan. The frequency of GDM consequently increased 2–4-fold as compared with the previous criteria [10], i.e., meeting at least two of three threshold values from a 75-g oral glucose tolerance test (OGTT); fasting glucose ≥100 mg/dL, 1-h postprandial glucose ≥180 mg/dL, and 2-h postprandial glucose ≥150 mg/dL, as proposed by the Japan Society of Obstetrics and Gynecology (JSOG) [11]. These criteria are similar to those proposed by the IADPSG (meeting at least two of three threshold values from a 75-g OGTT; fasting plasma glucose ≥92 mg/dL, 1-h plasma glucose ≥180 mg/dL, and 2-h plasma glucose ≥153 mg/dL) [10] and the American Diabetes Association (meeting at least two of three threshold values from a 75-g OGTT; fasting plasma glucose ≥95 mg/dL, 1-h plasma glucose ≥180 mg/dL, and 2-h plasma glucose ≥155 mg/dL) [12]. Among women with newly diagnosed GDM, most had only one abnormal value (OAV) based on the JSOG criteria [our unpublished data, under submission]. A multi-institutional retrospective review was thus performed by the Japan GDM Study Group (JGSG) to assess whether the treatment of mild GDM, i.e., one abnormal OGTT value, improves pregnancy outcomes in Japan.

2. Materials and methods

2.1. Study design

The present retrospective study was conducted in 30 general hospitals in Japan from 2005 to 2010. The protocol was approved by the ethics committee at each of the 30 collaborating centers. All women with a singleton pregnancy and no prior diagnosis of diabetes mellitus were included. Women with multi-fetal gestations, pre-gestational diabetes, previous treatment for gestational diabetes or an active chronic systemic disease other than chronic hypertension, and those with the second of two pregnancies in the same year