Ⅱ．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
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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
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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
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和栗雅子	GDMのリスクと重症化予防	臨床助産ケア	2014 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	１章　わが国の糖尿病の動静とその背景（４）肥満　B. 肥満妊娠の合併症	難波光義、杉山隆	「妊娠と糖尿病」母児管理のエッセンス	金芳堂	2013	21-26
安日一郎	５章　糖代謝異常妊娠の管理　§４　糖代謝異常妊娠の管理（９）分娩：分娩時期と分娩管理	難波光義、杉山隆	「妊娠と糖尿病」母児管理のエッセンス	金芳堂	2013	204-211
宮越敬，池ノ上学，春日義史，et al.	妊娠時の代謝の変化 1.母体の変化A.糖代謝の変化 2)インスリン感受性の観点から	難波光義、杉山隆	「妊娠と糖尿病」母児管理のエッセンス	金芳堂	2013	38-42
宮越敬，税所芳史，吉村泰典	ホルモン療法実践マニュアル「糖尿病・妊娠糖尿病」	青木大輔，金山尚裕，百枝幹雄，若槻明彦	産科と婦人科	診断と治療社	2013	57-66
和栗雅子	【先天異常．糖代謝異常妊娠の合併症】胎児合併症	難波光義、杉山隆	「妊娠と糖尿病」母児管理のエッセンス	金芳堂	2013	118-122
和栗雅子	【糖代謝異常妊娠の管理】運動療法	難波光義、杉山隆	「妊娠と糖尿病」母児管理のエッセンス	金芳堂	2013	188-194
和栗雅子	【当センターにおけるGDMフォロー　糖代謝異常妊娠の管理】GDMのフォロー	難波光義、杉山隆	「妊娠と糖尿病」母児管理のエッセンス	金芳堂	2013	217-220
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

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
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

Ⅲ. 研究成果の刊行物・別刷

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CORRESPONDENCE

Response to Metoki

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We thank Dr Metoki for his thoughtful comments.[1] He raises the important points that mid-pregnancy fall may have an impact on the occurrence of pregnancy-induced hypertension (PIH) and that seasonal variations in blood pressure (BP) may affect the BP changes during pregnancy and contribute to the occurrence of PIH. We assessed clinic BP values at week 30 and at a time after week 34 in healthy pregnant women who participated in the previous study.[2] As shown in Figure 1, a decreasing BP in the second trimester was observed. Because pregnant women with low BP at week 20 had less risk of PIH,[2] even if these women had high BP at week 16, a mid-pregnancy fall in BP is thought to be inversely correlated with the occurrence of PIH. As suggested by Metoki *et al.*,[3] endothelial function may contribute to the relationship between the mid-pregnancy fall in BP and the occurrence of PIH. In addition, we assessed the seasonal trend in BP changes during pregnancy. As shown in Table 1, pregnant women who delivered in the hot season (May to October, average daily temperature $\geqslant 15\,^{\circ}C$ in Tokyo) had higher BPs before 16 weeks and at 20 weeks of gestation than those who delivered in the cold season (December to April, average daily temperature $< 15\,^{\circ}C$ in Tokyo). By contrast, pregnant women who delivered in the cold season tended to have a higher BP at 30 weeks and after 34 weeks than those who delivered in the hot season. These results suggest that seasonal changes in temperature may affect clinic BP values during pregnancy. However, the occurrence of PIH was unaffected by the seasonal trend in BP changes. The odds ratio of PIH in pregnant women who delivered in the cold season was 0.63 compared with that in pregnant women who delivered in the hot season; this is statistically insignificant.

Consistent with previous studies showing that home BP fell from the first trimester to the second trimester and then continued to increase until the time of delivery,[3] and that pregnant women who delivered in winter tended to have higher home BPs than those who delivered in summer,[4] we confirmed the mid-pregnancy fall in BP and the seasonal trend in BP changes during pregnancy even if BPs are measured at the clinic. We hope that our study will inspire researchers to further examine the effects of the mid-pregnancy fall in BP and the seasonal trend in BP changes during pregnancy on predicting the risk of PIH.

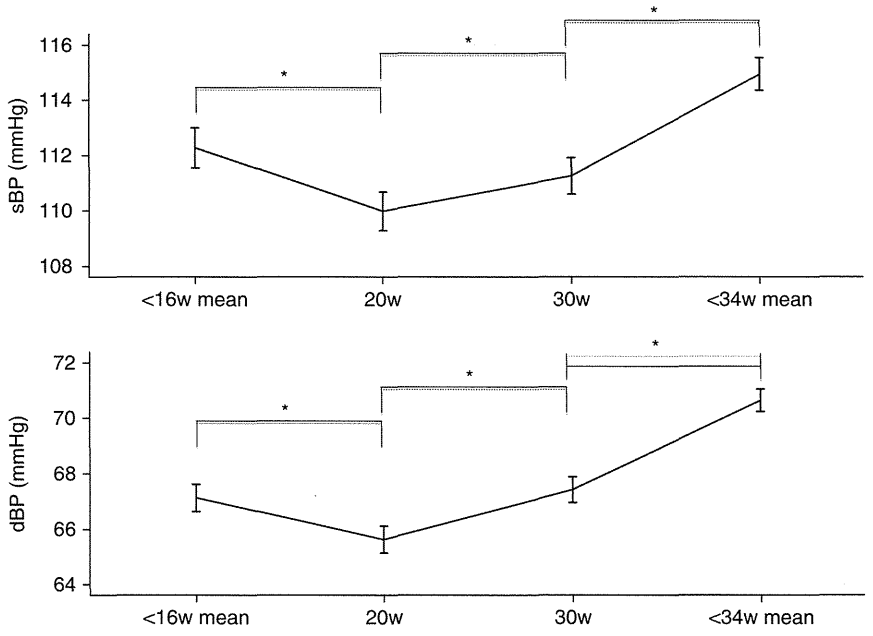

Figure 1 Systolic/diastolic blood pressure (sBP/dBP) in 976 pregnant women. *$P<0.0001$.

Table 1 BP values and OR (95% CI) of PIH stratified by season in 976 pregnant women

	EDC_Hot season (n = 503)		*EDC_Cold season (n = 473)*		P-value
Systolic BP					
Before 16 weeks of gestation	114.0	11.9	110.4	10.9	<0.0001
20 weeks of gestation	111.6	11.6	108.3	10.4	<0.0001
30 weeks of gestation	110.6	10.1	111.9	11.0	0.059
After 34 weeks of gestation	114.4	9.7	115.5	9.1	0.073
Diastolic BP					
Before 16 weeks of gestation	67.8	8.4	66.4	7.5	0.009
20 weeks of gestation	66.4	7.8	64.8	7.4	0.001
30 weeks of gestation	66.8	7.1	68.1	7.5	0.004
After 34 weeks of gestation	70.2	6.5	71.1	6.4	0.052
PIH	Reference		0.63	(0.30–1.3)	0.21

Abbreviations: BP, blood pressure; CI, confidence interval; EDC, estimated date of confinement; OR, odds ratio; PIH, pregnancy-induced hypertension.
BP values are given as mean (s.d.).
Occurrence of PIH is given as OR and 95% CI.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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OBSERVATIONS

Antepartum Oral Disposition Index as a Predictor of Glucose Intolerance Postpartum

Although women with gestational diabetes mellitus (GDM) have an increased subsequent risk for diabetes, the diabetic risk might be heterogeneous because the degree of abnormal glucose metabolism varies. The glucose tolerance status in pregnancy is related with postpartum prediabetes or diabetes, whereas studies on the antepartum factors associated with dysglycemia postpartum are limited (1,2). Women with GDM should be screened for diabetes postpartum; however, some miss the follow-up for the glucose surveillance.

β-Cell function contributes to the development of glucose intolerance, and the oral glucose tolerance test (OGTT)-derived measures for β-cell function (i.e., oral disposition index [DIo]) seem to be predictive of developing diabetes (3). Likewise, the DIo during pregnancy might have potential to predict glucose intolerance postpartum. Therefore, we investigated the relation between antepartum DIo and postpartum glucose tolerance status in women with GDM.

With the approval of the institutional review board, the medical records were reviewed for 53 sequential women with GDM who were followed by postpartum OGTT between 2004 and 2010. Each woman underwent a two-step screening for GDM: universal early testing in women with high-risk characteristics and a standard 1-h 50-g oral glucose challenge test between 24 and 27 weeks' gestation for those not previously found to have glucose intolerance. Women with positive screen underwent a 75-g OGTT with the measurement of plasma glucose (mg/dL) and insulin concentration (mU/L) at basal, 30, 60, and 120 min after the glucose load. GDM was diagnosed by the criteria of the Japan Diabetes Society (4). Three to six months postpartum, the repeat OGTT characterized glucose tolerance status in women with recent GDM into the following categories by the Japan Diabetes Society criteria: diabetic, borderline, and normal (4). We calculated the antepartum DIo using the following measures: insulin secretion–sensitivity index-2 (ISSI-2) and insulinogenic index (IGI)/fasting insulin (5).

Compared with normal glucose tolerance (NGT; $n = 35$), women with glucose intolerance postpartum ($n = 18$: diabetes 3, borderline 15) demonstrated significantly lower levels of antepartum ISSI-2 (mean ± SD, 1.32 ± 0.38 vs. 1.69 ± 0.50; $P < 0.01$). There were significant differences in antepartum IGI/fasting insulin between the glucose intolerance postpartum and NGT groups (0.069 ± 0.045 vs. 0.109 ± 0.074, respectively; $P < 0.01$). After adjustment for pregravida BMI, family history of diabetes, glycemic profiles during pregnancy (i.e., plasma glucose levels during the OGTT and HbA_{1c}), antepartum ISSI-2 was still a negative correlate of glucose intolerance postpartum ($P < 0.05$). On receiver operating characteristic (ROC) analysis, the best predictor for glucose intolerance postpartum was ISSI-2 ≤1.44 (the area under the ROC curve [95% CI], 0.73 [0.59–0.87]: sensitivity of 61% and specificity of 80%).

This is the first report highlighting a potential role of the antepartum DIo to predict postpartum glucose intolerance. The adoption of the new criteria of GDM would result in the increased number of the affected women. Our findings suggest that antepartum DIo could help to identify those at highest risk of glucose intolerance postpartum and warrant further study of the appropriate follow-up strategy in GDM by the new criteria.

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Y.S. and K.Miy. researched data, wrote the manuscript, contributed to discussion, and reviewed and edited the manuscript. M.T., T.M., K.Min., Y.Y., and H.I. contributed to discussion and reviewed and edited the manuscript. K.Miy. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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AOGS
ACTA Obstetricia et Gynecologica Scandinavica

AOGS LETTER TO THE EDITOR

Fetal growth and gestational hypertension in women classified as gestational diabetes mellitus defined by the new consensus criteria only

Sir,

Since the new consensus criteria for gestational diabetes mellitus (GDM) were proposed by the International Association of Diabetes and Pregnancy Study Groups based on the results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, several studies have demonstrated that women with GDM by the new criteria are at high risk of large for gestational age (LGA) and gestational hypertension (GH) (1–4). For instance, O'Sullivan et al. demonstrated the clinical feature of the new consensus criteria in a predominantly European population (3). However, it remains to be determined whether similar perinatal complications are achieved in clinical practice as much as in research settings. In particular, data on perinatal outcomes in women who were classified as having normal glucose tolerance (NGT) by the previous criteria, but as having GDM by the new criteria (i.e. the new criteria only-defined GDM), are limited. In addition, the majority of participants in the HAPO study were of non-Asian ethnicity, making it difficult to interpret the results in a Japanese population. With this background, we have investigated the clinical impact of the new criteria on perinatal outcomes in a Japanese setting.

A retrospective review of medical records was performed for 5749 sequential Japanese women who were cared for at our hospital between 1996 and 2010. Each woman underwent a two-step screening for GDM: universal early testing in women with high-risk characteristics and a standard one hour, 50 g oral glucose challenge test between 24 and 27 weeks of gestation for all women not previously found to have glucose intolerance. Women with positive screening underwent a two hour 75 g oral glucose tolerance test. On the basis of the criteria proposed by the Japan Society of Obstetrics and Gynecology (JSOG), GDM was diagnosed if two or more values reached or exceeded the following thresholds: fasting, 5.6 mmol/L; one hour, 10.0 mmol/L; and two hours, 8.3 mmol/L (5). All women with GDM were treated with a strict glycemic protocol.

Using the new criteria (1), 349 (6.1%) women were reclassified into hyperglycemia in pregnancy (overt diabetes 3; GDM 346), compared with 132 (2.3%) by the JSOG criteria. Compared with the 'new criteria-defined NGT', those with GDM by the new criteria had a higher incidence of LGA births (12.2 vs. 6.2%, $p<0.001$) and GH (4.1 vs. 1.8%, $p<0.01$). The 'new criteria only-defined GDM' corresponding to untreated mild hyperglycemia ($n=217$) showed a significantly higher incidence of LGA and GH, compared with the 'new criteria-defined NGT' (Table 1). After adjustment for maternal age, pre-pregnancy body mass index, previous GDM, a family history of diabetes and the glucose intolerance status using a

Table 1. Clinical characteristics of women reclassified into gestational diabetes mellitus defined by the new consensus criteria only.

Parameter	Units	The new criteria-defined NGT ($n=5400$)	The new criteria only-defined GDM ($n=217$)	p-Value
Age	(years)	33±5	36±4	<0.0001
Body mass index	(kg/m^2)	20.3±2.5	21.2±3.0	<0.0001
Overweight (body mass index ≥25 kg/m^2)	(%)	4.9	9.7	0.002
Underweight (body mass index <18.5 kg/m^2)	(%)	21.3	15.8	0.053
Parous	(%)	30.1	31.3	0.704
Previous GDM	(%)	0.48	1.38	0.100
Family history of DM	(%)	6.48	17.05	<0.0001
GW at delivery	(week)	39±2	38±2	0.020
Birthweight	(g)	2954±464	2956±522	0.960
Macrosomia	(%)	0.63	0.92	0.649
GH	(%)	1.86	4.61	0.008
Pre-eclampsia	(%)	1.83	1.38	1.000
LGA	(%)	6.22	11.52	0.002
SGA	(%)	9.04	8.76	0.887

Abbreviations and definitions: DM, diabetes mellitus; GDM, gestational diabetes mellitus defined by the former criteria; GH, gestational hypertension; GW, gestational week; macrosomia, defined as birthweight >4000 g; LGA, large for gestational age, defined as birthweight >90th percentile for gestational age; NGT, normal glucose tolerance defined by the new criteria; and SGA, small for gestational age, defined as birthweight <10th percentile for gestational age. Continuous variables are given as means±SD. Statistical analysis: Student's t-test for continuous variables and the chi-squared or Fisher's exact test for categorical variables.

Letter to the Editor

multiple linear regression model, the 'new criteria only-define GDM' was correlated with LGA and GH (adjusted odds ratio 1.76 and 2.20; 95% confidence interval 1.14–2.71 and 1.13–4.28, respectively). Our results suggest that women with GDM defined by the new consensus criteria only are at high risk of subsequent development of GH as well as LGA.

Currently, a number of healthcare associations in the world are contemplating the adoption of the new criteria. Based on our findings, the new criteria appear to be acceptable to a Japanese clinical setting with regard to LGA and GH. As discussed in several articles (3,4), however, further studies are warranted to determine the cost-effective therapeutic strategies for treatment of GDM defined by the new criteria.

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Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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ORIGINAL

Marked decline in beta cell function during pregnancy leads to the development of glucose intolerance in Japanese women

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Abstract. The aim of this study is to investigate glucose metabolism longitudinally during pregnancy to explore mechanisms underlying gestational diabetes mellitus (GDM). We reviewed a total of 62 pregnant Japanese women who underwent a 75g oral glucose tolerance test (OGTT) twice during pregnancy (median: early, 13; late, 28 weeks' gestation) because of positive GDM screening. All showed normal OGTT results in early pregnancy. Based on late OGTT, 15 had GDM (late-onset GDM) and 47 normal glucose tolerance (NGT). In early pregnancy, there were no significant differences in insulin sensitivity (insulin sensitivity index derived from OGTT [IS_{OGTT}] and homeostasis model assessment for insulin resistance [HOMA-IR]) and insulin secretion (a ratio of the total area-under-the-insulin-curve to the total area-under-the-glucose-curve [$AUC_{ins/glu}$] and insulinogenic index [IGI]) between the NGT and late-onset GDM groups. In each group, insulin sensitivity significantly decreased from early to late pregnancy, most in the late-onset GDM group (each $p < 0.05$). The insulin secretion showed no significant changes with advancing pregnancy in both of the groups, although late-onset GDM showed significantly lower IGI compared with NGT in late OGTT ($p < 0.05$). When assessed beta cell function by OGTT-derived disposition index (*i.e.* Insulin Secretion-Sensitivity Index-2 and IGI/fasting insulin), the indices significantly decreased from early to late pregnancy in the both groups (each $p < 0.05$). Women with late-onset GDM showed significantly lower indices compared with NGT (each $p < 0.05$). The failure of beta cell to compensate for decreased insulin sensitivity could contribute to the development of the late-onset GDM.

Key words: Insulin sensitivity, Insulin secretion, Disposition index, Glucose metabolism, Pregnancy

IT HAS BEEN widely recognized that insulin sensitivity decreases as pregnancy advances, reaching the nadir in the third trimester [1]. When insulin secretion fails to compensate for the escalated insulin needs during pregnancy, pregnant women are diagnosed to have gestational diabetes mellitus (GDM)[2]. To date, studies on glucose metabolism in pregnant women have shown impaired beta cell function in GDM [3, 4, 5]. As a consequence, beta cell dysfunction is thought to be a potential etiology of GDM [6].

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Several prospective studies in Caucasian population have demonstrated that beta cell function could deteriorate from early to late pregnancy in women with normal glucose tolerance as well as GDM [1, 7]. Especially, women diagnosed with GDM in late pregnancy (*i.e.* late-onset GDM) showed marked decline in beta cell function during pregnancy [3, 5]. This observation might be one explanation that women with a history of GDM are at high risk for the future glucose intolerance (*i.e.* type 2 diabetes) on a background of chronic insulin resistance. However, data on longitudinal changes in glucose metabolism of pregnant Japanese women are unavailable because only cross-sectional studies have been reported [5].

In the current study, we retrospectively examined the glucose metabolism of pregnant Japanese women. Using a cohort of pregnant women undergoing oral