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Time course of metabolic status in pregnant women: The Japan Environment and Children's Study

Hatoko Sasaki[1]*†, Naoko Arata[1], Ai Tomotaki[1,2], Kiwako Yamamoto-Hanada[1], Hidetoshi Mezawa[1], Mizuho Konishi[1], Kazue Ishitsuka[1], Mayako Saito-Abe[1], Miori Sato[1], Minaho Nishizato[1], Hirohisa Saito[1], Yukihiro Ohya[1], Japan Environment and Children's Study (JECS) Group‡

[1]National Center for Child Health and Development, Tokyo, Japan, and [2]National Center for Global Health and Medicine/National College of Nursing, Tokyo, Japan

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***Correspondence**
Hatoko Sasaki
Tel.: +81-3-3416-0181
E-mail address:
sasaki-ht@ncchd.go.jp

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ABSTRACT

Aims/Introduction: We aimed to evaluate the metabolic status of pregnant women by assessing metabolic biomarkers of participants in the Japan Environment and Children's Study, a nationwide, multicenter, pregnancy and birth cohort.

Materials and Methods: Pregnant women aged 14–50 years were studied in 15 centers across Japan. Clinical information was obtained using self-administered questionnaires. Blood samples were taken during the first two trimesters to measure metabolic biomarkers. Samples were divided into seven groups according to the weeks of pregnancy.

Results: Among 82,972 pregnant women, 43 had only type 1 diabetes, 78 had only type 2 diabetes, 2,315 had only gestational diabetes and 354 had only dyslipidemia. Glycated hemoglobin, total cholesterol, low-density lipoprotein cholesterol and triglyceride across all the percentiles increased as prepregnancy body mass index increased, whereas high-density lipoprotein cholesterol levels across all the percentiles decreased as body mass index increased. Glycated hemoglobin was high in participants with type 1 diabetes or type 2 diabetes only, but not in those with gestational diabetes or hyperlipidemia only. Participants with type 2 diabetes or dyslipidemia only had high triglyceride in the first trimester, which then decreased in the second trimester. Participants with type 2 diabetes only also showed low high-density lipoprotein cholesterol, whereas participants with dyslipidemia only showed high total cholesterol and low-density lipoprotein cholesterol throughout.

Conclusions: Metabolic biomarkers were affected by blood sample timing and underlying metabolic disease. The Japan Environment and Children's Study will clarify the influences of metabolic status during pregnancy on the health and development of the offspring in future studies.

INTRODUCTION

The glucose and lipid metabolism of women is known to change during pregnancy. Insulin resistance increases during pregnancy because of an increased secretion of hormones, such as placental growth hormone, that promote the transplacental transport of glyconutrients to the fetus[1]. Because pregnant women use lipids as an energy source, the plasma levels of cholesterol and triglyceride in pregnant women are relatively high[2]. In contrast, earlier research has suggested that the timing of blood collection during different stages of pregnancy is an important point to consider. Because of the changes in lipid profile during the second and third trimesters, other factors including pregnancy-related complications and/or placenta dysfunction might impede interpretation regarding cause or consequence[3]. Pregnant women with obesity are at risk of many complications, including stillbirth, large-for-gestational-age infants and associated complications at birth[4]. Children born to

†Present address: Medical Support Center civironment and Children's Study (JECS), National Center for Child Health and Development, Tokyo, Japan.
‡Japan Environment and Children's Study (JECS) Group members are listed in Acknowledgments.
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women with higher maternal prepregnancy Body mass index (BMI) and excess gestational weight gain could themselves be at risk of childhood obesity[5]. Identifying women at risk allows initiation of risk-specific treatment and tailored care during pregnancy.

In the present study, we analyzed data collected from pregnant women who participated in a nationwide birth cohort study (the Japan Environment and Children's Study [JECS]), using a questionnaire and blood samples taken during the first or second trimester of pregnancy, to evaluate their metabolic status. This is the first study to describe the metabolic status of a large cohort of pregnant women aged 14–50 years and living in Japan.

METHODS

Overview

The JECS is a prospective nationwide birth cohort study that was launched by the Japanese Ministry of the Environment. The JECS covers a wide geographical area of Japan and comprises 15 regional centers (Hokkaido, Miyagi, Fukushima, Chiba, Kanagawa, Koshin, Toyama, Aichi, Kyoto, Osaka, Hyogo, Tottori, Kochi, Fukuoka and South Kyushu/Okinawa). Participants were pregnant women and their partners who were recruited during their early pregnancy from hospitals or local government offices when the maternal and child health handbook was provided. The main aim of the JECS was to evaluate whether environmental factors, such as chemicals, physical activity and lifestyle, influence childhood health. The health of mothers reflects genetic factors and lifestyle, and one of the important themes of the study is to establish how the health of mothers during pregnancy affects the subsequent health of their child. Recruitment began in January 2011, and the number of pregnant women enrolled reached 100,000 in March 2014[6]. Participating children are expected to remain in the study until they reach 13 years of age.

Ethical approval

The JECS was carried out based on the Ethical Guidelines for Epidemiological Research published by the Japanese Ministry of Health and Welfare (now the Ministry of Health, Labor and Welfare). The JECS protocol was reviewed and approved by the Japanese Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all the participating institutions. Written informed consent was obtained from all participants.

Recruitment

The eligibility criteria for participants in the JECS were as follows: (i) the participant should reside in the study area at the time of recruitment and expect to continue to reside in Japan for the foreseeable future; (ii) their expected delivery date should be between 1 August 2011 and mid-2014; and (iii) the participant should be capable of participating in the study without difficulty; that is, they must be able to understand the Japanese language and complete the self-administered questionnaire.

Either or both of the following two recruitment protocols were applied: (i) recruitment at the time of first prenatal examination at cooperating health care providers such as obstetric facilities, and/or (ii) recruitment at local government offices issuing pregnancy journals, namely Mother-Child Health Handbooks (the Mother-Child Health Handbook is an official booklet that all expecting mothers in Japan are given complimentary when they become pregnant in order to receive municipal services for pregnancy, delivery and childcare)[6]. The study population contained 104,102 fetal records.

Assessment of clinical information

Information about the week of pregnancy was obtained from pregnant participants using an initial self-administered questionnaire during the second or third trimester of pregnancy. The height and weight of each mother before pregnancy and the maternal age at registration were obtained either from the participant's doctors or from a self-administered questionnaire. The lifetime prevalence of diabetes and other endocrine disorders, including complications of type 1 diabetes, type 2 diabetes, gestational diabetes (GDM) and dyslipidemia, was also assessed based on the diagnoses made by the participant's doctors and the initial self-administered questionnaire.

Screening tests for all pregnant women for GDM and "overt diabetes in pregnancy" are carried out in Japan, using the following stepwise method[7]:

1. Measure random blood glucose level in the first trimester (each hospital should determine its own cut-off value). Before planning a 75-g oral glucose tolerance test for women with a random blood glucose level of 200 mg/dL, check: (i) fasting plasma glucose 126 mg/dL; (ii) glycated hemoglobin (HbA1c) 6.5%, expressed as National Glycohemoglobin Standardization Program value; and (iii) definite diabetic retinopathy for differential diagnosis of "overt diabetes in pregnancy."
2. Give the pregnant woman a 50-g glucose challenge test (cut-off value 140 mg/dL) or measure the random blood glucose level a second time (cut-off value 100 mg/dL) between 24 and 28 gestational weeks in women not diagnosed as having GDM or "overt diabetes in pregnancy."
3. A 75-g oral glucose tolerance test is given to all women with a positive screening test result, except women diagnosed as having "overt diabetes in pregnancy" and GDM is diagnosed with International Association of Diabetes and Pregnancy Study Groups criteria[8]. "Overt diabetes in pregnancy" is classified as type 2 diabetes.

The screening method for GDM described in the guideline[7,8] was also used at the time the present study was carried out. It is reported that the prevalence of GDM was approximately 8.5% when the 75-g oral glucose tolerance test was given to all pregnant women[9].

Biomarker assays

Non-fasting blood samples were obtained from pregnant women during their second or third trimester of pregnancy. The following biomarkers were assayed by a contract clinical laboratory (SRL, Inc., a commercial laboratory in Tokyo, Japan): HbA1c (National Glycohemoglobin Standardization Program) was measured using a high-performance liquid chromatographic method; serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) were analyzed enzymatically using a 7700 clinical chemistry/immunoassay hybrid analyzer (Hitachi High-Technologies Co., Ltd, Tokyo, Japan).

Exclusion of study participants

We prespecified that pregnant participants whose data for HbA1c, Hb, TC, LDL-C, HDL-C or TG were missing or below the quantifiable range in the transcripts of medical records would be excluded. Participants who had missing data or results outside the reference range for other variables, or those who had other endocrine disorders, were also excluded from subsequent analyses.

Statistical analysis

We used the data from individuals in the first and second trimesters with no missing values. The distribution of each biomarker was summarized according to the prepregnancy BMI and maternal age at registration, according to the week of pregnancy (the first trimester was divided into 4–7, 8–11 and 12–13 weeks, and the second trimester into 14–15, 16–19, 20–23 and 24–27 weeks), and according to the presence or absence of diabetes or other endocrine disorders. Each woman was evaluated only once during pregnancy. Each biomarker was summarized using the 2.5th, 25th, 50th, 75th and 97.5th percentiles. The presence or absence of diabetes and other endocrine disorders was also summarized according to the prepregnancy BMI. Descriptive analysis was carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA) and SPSS statistics 25.0 (IBM, Chicago, IL, USA) [10].

RESULTS

The present study contained 80,636 pregnant women, including 4,611 women with diabetes, dyslipidemia or endocrine disorders, while excluding women with missing data. A summary of the 80,636 participants is shown in Figure 1. There were 43 participants with type 1 diabetes only, 78 with type 2 diabetes only, 2,315 with GDM only, 354 with dyslipidemia only and 1,821 with other endocrine disorders (including complications of type 1 diabetes, type 2 diabetes, GDM or dyslipidemia). Blood samples were obtained from 32,132 healthy participants during the first trimester of pregnancy and from 43,893 healthy participants during the second trimester of pregnancy.

Table 1 describes the distribution of metabolic biomarkers in healthy participants according to their prepregnancy BMI and age at registration. Across all the percentiles, the levels of HbA1c, TC, LDL-C and TG elevated as BMI increased, whereas that of HDL-C decreased as BMI increased. The levels of HbA1c and HDL-C across all the percentiles slightly increased with the advance of age. The levels of TC, LDL-C and TG across all the percentiles increased with the advance of age, except among participants aged <20 years. Table 2 shows the distribution of metabolic biomarkers in healthy participants according to the week of pregnancy during which blood samples were collected. HbA1c levels did not differ substantially between the first and second trimesters. The serum levels of all lipid biomarkers (TC, LDL-C, HDL-C and TG) across all the percentiles increased as pregnancy progressed.

Table 3 shows a comparison of the distribution of metabolic biomarkers between participants with and without diabetes or other endocrine disorders. HbA1c was higher in participants with type 1 diabetes, type 2 diabetes or GDM only than in healthy participants. Furthermore, HbA1c was higher than the recommended target of 6.5%[1] for glycemic control during pregnancy in 39.5% of those with type 1 diabetes only and 24.3% of those with type 2 diabetes only.

Our evaluation of lipid biomarkers showed that participants with type 1 diabetes had slightly better lipid profiles than healthy participants. Lipid profiles in participants with type 2 diabetes were characterized by higher TG levels and lower HDL-C during the first trimester of pregnancy, and a slight increase in lipid levels between the first and second trimesters. TG levels were higher in participants with GDM than in healthy participants, but no differences in the distribution of cholesterol levels, including HDL-C, were observed between these groups. In participants with dyslipidemia, the distribution of HDL-C was similar to those of healthy participants, whereas TC, LDL-C and TG levels were higher than those of healthy participants.

Participants with higher prepregnancy BMI were more likely to have diabetes or endocrine disorders (Table S1).

DISCUSSION

This is the first report of the metabolic profiles of pregnant women, which was based on big data extracted from questionnaires and blood samples taken during pregnancy, obtained from a nationwide large cohort study across Japan. We report changes in the distribution of metabolic biomarkers with the progression of pregnancy, and differences in the distribution of those biomarkers between healthy pregnant women and pregnant women with diabetes or other metabolic disorders.

According to previous reports, HbA1c levels decrease during the second trimester of pregnancy and increase during the third trimester[11,12]. The participants in the present study also showed a decrease in HbA1c between the first and second trimesters.

HbA1c was higher in participants with pregestational diabetes (type 1 diabetes or type 2 diabetes) or GDM than in healthy participants. Approximately half of the participants had HbA1c levels that were less than the recommended target of 6.5% for glycemic control during pregnancy[13], whereas >5.0% had HbA1c levels that were higher than the generally

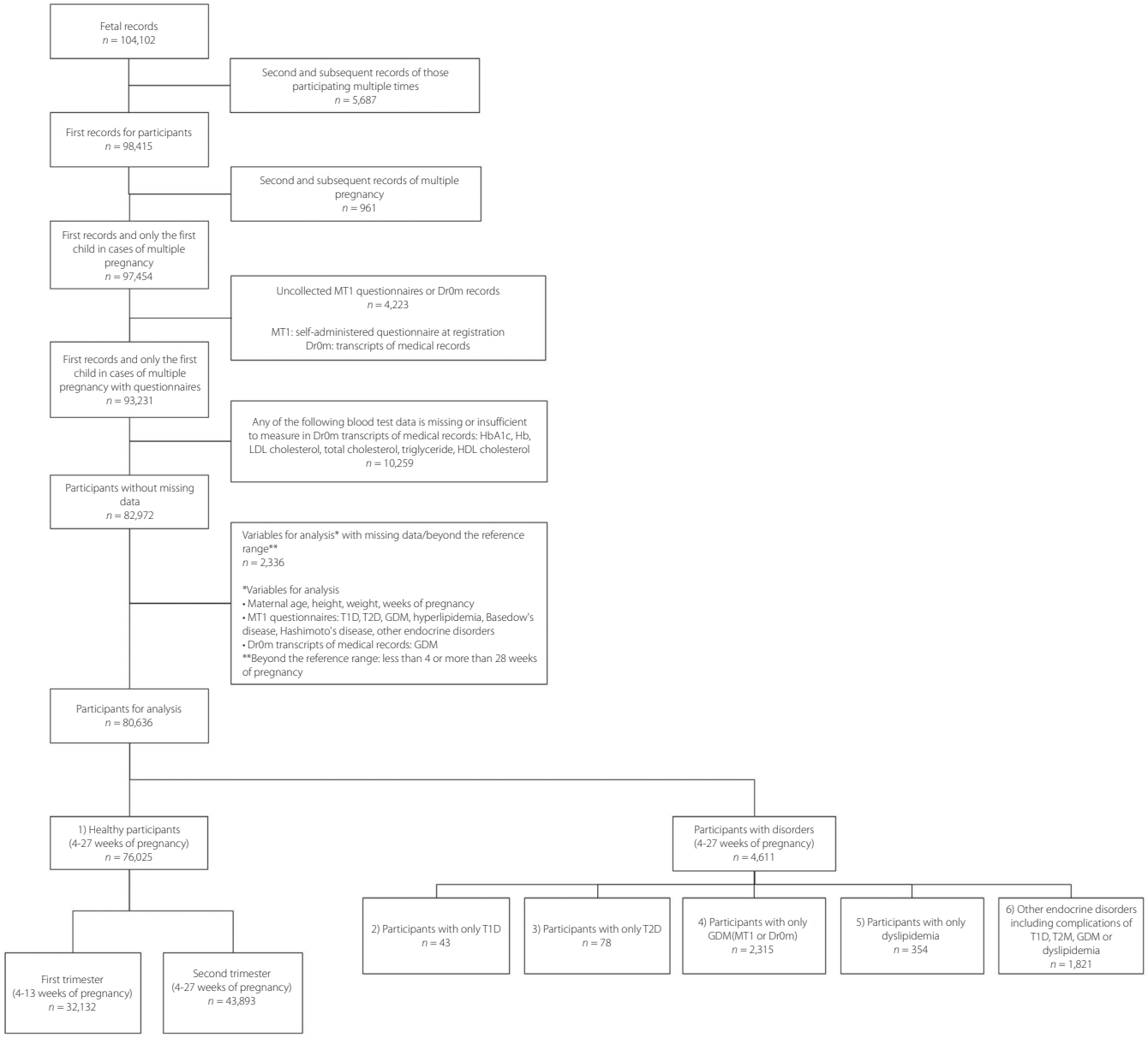

Figure 1 | Flow chart characterizing the study participants and reasons for their exclusion. GDM, gestational diabetes; T1D, type 1 diabetes; T2D, type 2 diabetes.

recommended target of 7.0% as an indicator of glycemic control in the Japanese population[14]. This observation led us to speculate that our participants often conceived without planning and while their glycemic control was poor.

It is known that levels of cholesterol and TG increase during pregnancy[2], and this study also showed that levels of all lipid biomarkers, including HDL-C, across all percentiles, increased as pregnancy progressed. However, the present results also showed that the second-highest TG level was found in the youngest age group (<20 years). This finding is inconsistent with another study that reported that TG levels were significantly higher in women of older ages[3]. Although the reason for the incongruent results between the present study and the previous study is uncertain, the fact remains that teenage pregnancy carries heightened risks for the mother and newborn. Despite the limitation that blood samples were not obtained after fasting, and were taken at any time, such samples should be informative, because the European Atherosclerosis Society recently recognized that it is not essential to use fasting blood samples to measure lipid profiles[15]. In addition, our sample size was sufficient to permit accurate statistical analysis.

Table 1 | Biomarkers classified by percentile in healthy pregnant participants according to body mass index before pregnancy and maternal age

	n	Adjusted HbA1c* (%)					Total cholesterol (mg/dL)					LDL cholesterol (mg/dL)					HDL cholesterol (mg/dL)					Triglyceride (mg/dL)				
		2.5th	25th	50th	75th	97.5th	2.5th	25th	50th	75th	97.5th	2.5th	25th	50th	75th	97.5th	2.5th	25th	50th	75th	97.5th	2.5th	25th	50th	75th	97.5th
BMI before pregnancy																										
<18.5	12,148	4.6	5.0	5.1	5.4	5.7	137	171	191	216	271	58	83	99	118	166	54	69	78	87	107	54	87	112	144	238
18.5–24	56,156	4.6	5.0	5.2	5.4	5.7	140	175	196	220	273	61	88	104	123	168	52	68	76	86	106	56	92	118	154	263
25–29	5,817	4.7	5.1	5.2	5.5	5.8	148	182	204	226	278	68	97	114	132	178	48	63	72	81	100	65	109	143	185	326
≥30	1,634	4.8	5.1	5.4	5.6	6.0	148	185	205	228	280	70	102	119	136	180	46	60	69	77	97	72	118	151	197	352
Maternal age at registration (years)																										
<20	786	4.5	4.8	5.0	5.2	5.5	139	175	194	217	266	66	92	108	126	168	48	64	72	80	102	62	97	127	166	293
21–24	7,590	4.6	4.9	5.1	5.2	5.6	136	171	193	216	270	60	86	103	122	169	51	66	75	84	104	54	90	117	153	258
25–29	22,680	4.6	5.0	5.1	5.3	5.6	140	173	194	217	271	61	87	103	122	167	52	67	76	85	105	55	89	115	150	260
30–34	26,771	4.7	5.0	5.2	5.4	5.7	141	175	197	221	274	61	88	104	124	170	52	68	76	86	106	57	93	119	156	270
35–39	15,607	4.7	5.1	5.2	5.4	5.8	142	178	199	224	276	61	90	106	126	171	52	68	77	86	107	59	96	124	162	276
≥40	2,591	4.7	5.1	5.3	5.5	5.8	145	182	203	227	278	66	93	110	128	175	52	68	76	86	106	60	100	129	168	288

*Adjusted glycated hemoglobin (HbA1c) is defined as HbA1c (National Glycohemoglobin Standardization Program) or calculated HbA1c = 1.02 × HbA1c (Japan Diabetes Society) + 0.25. BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2 | Biomarkers classified by percentile in healthy participants according to the week of pregnancy

Weeks of pregnancy	*n*	Adjusted HbA1c* (%)					Total cholesterol (mg/dL)					LDL cholesterol (mg/dL)					HDL cholesterol (mg/dL)					Triglyceride (mg/dL)				
		2.5th	25th	50th	75th	97.5th	2.5th	25th	50th	75th	97.5th	2.5th	25th	50th	75th	97.5th	2.5th	25th	50th	75th	97.5th	2.5th	25th	50th	75th	97.5th
First trimester of pregnancy																										
4–7 weeks	897	4.7	5.0	5.2	5.4	5.7	127	162	182	202	249	54	80	95	112	154	48	63	72	82	101	49	80	106	146	255
8–11 weeks	16,660	4.7	5.0	5.2	5.4	5.7	135	167	186	209	260	57	83	98	116	157	50	66	74	83	103	52	84	109	144	248
12–13 weeks	14,575	4.7	5.0	5.2	5.4	5.7	137	171	190	212	262	59	85	100	118	160	51	66	75	84	104	55	88	113	147	258
Second trimester of pregnancy																										
14–15 weeks	13,607	4.7	5.0	5.2	5.4	5.7	142	175	196	218	269	62	88	104	123	166	52	67	76	85	105	58	93	119	154	263
16–19 weeks	19,725	4.6	5.0	5.1	5.4	5.7	147	182	203	227	278	65	93	109	128	173	53	69	78	87	108	62	98	126	162	275
20–23 weeks	7,883	4.6	4.9	5.1	5.3	5.7	148	189	211	235	288	67	97	115	135	181	54	70	79	89	108	64	103	133	171	294
24–27 weeks	2,678	4.6	4.9	5.1	5.3	5.7	147	188	211	239	303	67	96	115	138	192	53	70	79	88	110	61	103	133	176	314
Overall	76,025	4.7	5.0	5.2	5.4	5.7	135	168	188	210	261	58	84	99	117	158	51	66	74	83	103	53	86	111	146	253

*Adjusted glycated hemoglobin (HbA1c) is defined as HbA1c (National Glycohemoglobin Standardization Program) or calculated HbA1c = 1.02 × HbA1c (Japan Diabetes Society) + 0.25. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3 | Distribution of biomarkers in pregnant participants with or without diabetes/endocrine disorders

Variables	Trimester of pregnancy	Healthy participants					Participants with type 1 diabetes only					Participants with type 2 diabetes only					Participants with gestational diabetes only					Participants with dyslipidemia only				
		n = 32,136 (1st), 43,899 (2nd)					*n* = 28 (1st), 15 (2nd)					*n* = 35 (1st), 43 (2nd)					*n* = 1,002 (1st), 1,313 (2nd)					*n* = 149 (1st), 205 (2nd)				
		2.5th	25th	50th	75th	97.5th	2.5th	25th	50th	75th	97.5th	2.5th	25th	50th	75th	97.5th	2.5th	25th	50th	75th	97.5th	2.5th	25th	50th	75th	97.5th
Adjusted HbA1c* (%)	First	4.7	5.0	5.2	5.4	5.7	5.2	5.9	6.4	7.0	9.1	5.0	5.6	6.0	6.7	10.7	4.8	5.2	5.4	5.6	6.4	4.7	5.1	5.2	5.5	5.9
	Second	4.6	5.0	5.1	5.4	5.7	5.2	5.6	6.1	6.7	7.7	4.8	5.4	6.0	6.4	7.6	4.7	5.1	5.4	5.6	6.2	4.6	5.1	5.2	5.5	5.8
TC (mg/dL)	First	135	168	188	210	261	122	170	183	210	257	142	166	184	202	234	145	174	195	217	263	158	204	225	251	328
	Second	145	181	203	227	279	164	172	191	214	231	149	182	198	223	289	148	184	206	230	289	172	224	245	278	362
LDL-C (mg/dL)	First	58	84	99	117	158	50	75	93	104	142	61	84	95	124	145	64	89	107	124	166	83	113	124	156	232
	Second	64	92	109	128	174	68	90	91	117	148	57	95	105	128	176	66	96	112	132	181	79	126	144	174	261
HDL-C (mg/dL)	First	51	66	74	83	103	56	68	78	99	123	33	57	64	73	107	49	63	73	83	101	48	65	75	84	108
	Second	53	69	77	87	107	48	68	72	84	102	43	59	66	81	91	50	66	75	85	104	52	71	80	91	116
TG (mg/dL)	First	53	86	111	146	253	45	73	91	126	232	44	112	151	196	295	63	97	127	169	321	64	108	144	200	383
	Second	61	98	125	163	280	46	79	124	180	281	72	123	159	232	434	65	108	142	190	332	72	114	143	195	329

*Adjusted glycated hemoglobin (HbA1c) is defined as HbA1c (National Glycohemoglobin Standardization Program) or calculated HbA1c = 1.02 × HbA1c (Japan Diabetes Society) + 0.25.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

The levels of lipid biomarkers, excluding HDL-C, in participants with dyslipidemia were higher than those of healthy participants, as expected. Interestingly, participants with pregestational diabetes, in contrast to those with dyslipidemia, did not show higher levels of lipid biomarkers during the second trimester of pregnancy than healthy participants. This observation implies that pregnant women with pregestational diabetes are less likely to rely on lipids as an energy source because of their higher blood glucose levels. Participants with GDM reportedly have high TG levels and low HDL-C levels[16]. However, although the present study found that these participants had higher TG levels, their HDL-C levels were not different from those of healthy participants. The reason for the inconsistency between studies is unclear.

The present results concurred with those of a previous multi-institutional retrospective study of pregnancy outcomes of women with GDM according to pregestational BMI in Japan[17]. The previous study reported that GDM is more frequent among women with a higher prepregnancy BMI. Both maternal prepregnancy BMI and GDM have consistently been reported to be risk factors for obesity among offspring[5,18]. There is also growing evidence that GDM leads to adverse long-term maternal outcomes including type 2 diabetes and cardiovascular diseases[19,20]. Effective management of maternal diet and lifestyle factors is required before conception and during pregnancy to reduce the risks of morbidity for mothers and offspring. However, the effectiveness of providing dietary advice interventions during pregnancy lacks high-quality evidence[21]. We suggest that future trials should be designed to monitor adherence, consider women's views and preferences, and evaluate effects on both short- and long-term outcomes. More importantly, there is a need to measure and report on core outcomes for research on GDM[22].

The present study had several limitations. First, non-fasting blood samples could affect the evaluation of changes in lipid and other metabolic parameters during their second or third trimester of pregnancy. Second, blood samples were less frequently obtained from participants at 4–7 weeks of pregnancy and during the latter half of the second trimester (from 20 weeks of pregnancy) owing to a skewed distribution of the elapsed duration of pregnancy among the participants. However, our analyses were not adjusted for age or physique, as the purpose of this study was to describe the metabolic status of pregnant women. In further studies, we will examine associations between metabolic biomarkers, the elapsed duration of pregnancy, and the presence or absence of diabetic and endocrine disorders while adjusting for any confounding factors. Third, some of the clinical information used in this study was obtained from a self-administered questionnaire and might therefore have a limited reliability, given the likely variation in the diagnostic criteria and/or management strategies used. Additionally, the number of pregnant women with disorders or complications who enrolled in the present study were limited and might be insufficient, as our study was not a disease-

specific study, and could therefore have resulted in the low prevalence of metabolic disorders overall.

In summary, we have reported the time course of glucose and lipid metabolic biomarkers during pregnancy in Japanese women enrolled in the JECS. The distribution of these biomarkers was affected by the time of blood sample collection, as well as the presence or absence of underlying diseases. Monitoring pregnant women with poor glycemic and lipid profile is crucial to control and optimize these levels in reducing the risks of adverse pregnancy outcomes. In the future, the JECS will elucidate the influences of metabolic status during pregnancy on the health and development of the children born during the study.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Distribution of participants with or without diabetes/endocrine disorders by body mass index before pregnancy