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ORIGINAL ARTICLE

Folate intakes and folate biomarker profiles of pregnant Japanese women in the first trimester

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Objective: To assess the status of dietary folate intake, serum and red blood cell (RBC) folate, and related nutritional biomarkers in healthy Japanese women in early pregnancy.
Design: A cross-sectional, observational study.
Subjects: Pregnant women in the first trimester, at 7–15 weeks gestation ($n=70$), who were not consuming any folate supplements or folate fortified foods.
Methods: Three-day dietary records were obtained from each subject to assess dietary folate intake. Blood samples were collected for measurement of biomarkers. Biomarkers and nutrient intake were analyzed in two groups defined by their serum folate concentrations: the low folate group (serum folate <9 ng/ml) and the high folate group (serum folate $\geqslant 9$ ng/ml).
Result: Mean serum and RBC folate concentrations in all subjects were 10.3 and 519 ng/ml, respectively. These levels were remarkably higher than the reported values from many other countries despite our subjects receiving no folic acids supplements. However, mean folate intake by our subjects from natural foods was 289 μg/day, which is thought to be low according to the Japanese dietary recommendation specified for pregnant women. The intake of spinach and fruits was significantly greater in the high folate group than in the low folate group.
Conclusion: Folate intake was thought to be adequate to maintain a desirable level of serum folate concentration in Japanese pregnant women in the first trimester, although the intake of folate from natural food was not high enough to meet the recommended daily intake.
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Contributors: NM has contributed to data collection and analysis, the main investigation, and writing the paper. HT was involved in planning and coordinating the study, data collection and analysis, and produced the draft of the paper. KU was the supervisor and coordinator of the investigation. AI and KK were involved in data collection and analysis. SA, MY, HF and SO were responsible for selection of patients, and contributed to data collection. HI was involved in the study design. NY designed the study and was the overall supervisor of the project, and approved the manuscript.
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Introduction

It is well known that the periconceptional intake of folate is very important, as an adequate intake of folic acid will significantly reduce the risk of neural tube defects (NTDs). Many studies in Europe, China and the United States have shown that the periconceptional use of folic acid prevents NTDs (Berry *et al.*, 1999; Werler *et al.*, 1999; Ray *et al.*, 2002). In 2000, the Japanese government recommended that all women planning a pregnancy should consume an additional

400 μg/day of folate, referring to scientific evidence and recommendations in the other countries (Ministry of Health, Labour, and Welfare, Japan, 2005). Food fortification with folic acid is not popular in Japan, and the use of supplemental folic acid has not become widespread. Furthermore, there has been little awareness of this in Japan, and folate has not recently been added but was added 5 years ago to the 5th standard tables of food composition in Japan. Accordingly, there had not been fully investigated about folate intake and folate related biomarker in Japanese people. Recently, Kondo *et al.* (2005) reported folate intake and serum folate concentration in pregnant Japanese women including all trimesters. However, there are no studies on folate intake and folate-related biomarkers including RBC folate concentration in pregnant Japanese woman in the first trimester. For primary prevention of NTD, folate nutrient in early pregnancy is very important.

According to the National Nutrition Survey in Japan, dietary natural folate intake in young Japanese women is similar to the reported intake in the United States and in many other countries (Ministry of Health, Labour, and Welfare, Japan, 2001). As sources of folate in the Japanese diet may differ from those in other societies, it is necessary to assess folate levels in pregnant Japanese women, especially in early pregnancy, to evaluate the current Japanese diet in terms of adequacy of folate nutrition.

We conducted this study to investigate the association between folate intake and folate-related biomarkers (folate concentrations in serum and red blood cells (RBC)) in pregnant Japanese women who were not consuming any dietary folate supplements.

Methods

Study design and subjects

We selected two study sites in a public and a private hospital in the Tokyo Metropolitan Area, in cooperation with the Department of Gynecology. The public hospital is located in an uptown area and is a tertiary hospital with many patients referred from smaller clinics or hospitals in the local area. The private hospital is located in a downtown area and is a primary care hospital mainly specializing in gynecology. We have continued cross-sectional and longitudinal observational studies on pregnant women without major complications who visited the two hospitals in the period from February 2002 to March 2003, who agreed to participate in the surveys, and who gave written informed consent.

In this report we focused on subjects who were interviewed and examined in the first trimester. Of 106 subjects, 36 were excluded due to inadequate data for dietary intake, and five were excluded because they consumed folate supplements or folate fortified foods. A total of 70 subjects were included in this cross-sectional analysis, although only 50 of them had data for RBC folate concentration because RBC samples could not be collected from 20 subjects. The study protocol was approved by the Institutional Ethics Committee of the authors' affiliations.

Data collection of lifestyle and other background factors

A self-administered questionnaire was used to gather information on dietary habits, drinking, smoking and other background information, which was directly checked by interviewers in the survey suits. The height and prepregnancy body weight of the subjects were asked for in the questionnaire, while the current body weight was measured using a calibrated mechanical scale.

Dietary intake

Weighed dietary records were obtained from each subject for three nonconsecutive days within a week. Subjects were given detailed instructions by trained dietitians on how to weigh and record the consumed foods, using a colored instruction leaflet to illustrate the methods and examples. When the subjects visited the hospital for blood sampling, the dietitians checked all the recorded sheets and interviewed the subjects to clarify any ambiguous points.

The consumption of nutrients and foods was estimated from the records by a computerized dietary analysis program *Kokurakucho* (NTT Inc., Japan). A food composition database based on the Fifth Revision of the Standard Food Composition Table was incorporated in the dietary analysis program, which allowed for changes in nutrients during the cooking process (Watanabe *et al.*, 2003).

Blood sampling and analysis

Fasting blood samples were drawn for the measurement of hematological parameters (hemoglobin, hematocrit, and RBC count) and folate-related biomarkers. The measurements of biomarkers except for RBC folate were performed by SRL Inc. (Tokyo). Chemiluminescent immunoassay was used for the measurement of serum folate and vitamin B_{12}. High-performance liquid chromatography (HPLC) and enzyme immunoassay were used for the measurement of homocysteine and serum ferritin, respectively.

Whole blood was collected in a heparinized tube and preserved with 0.5% ascorbate solution for the measurement of RBC folate by microbiological assay using *Lactobacillus casei* ($n=50$) (Horne, 1997) based on previous reports. Samples were diluted with 0.05% ascorbic acid solution and preincubated for 30 min at 37°C for deconjugation of folate polyglutamates. Ninety six-well microplates were used for incubation of samples and medium containing *L. casei*. The plates were incubated for 48 h at 37°C. The optical density of each well was measured using a single wavelength of 570 nm. RBC folate level was then calculated from the mean whole-blood folate value by subtracting folate content of serum in the sample, and corrected by hematocrit value (Hoffbrand *et al.*, 1966).

Statistical analysis

Biomarkers and nutrient intake were analyzed in two groups according to the median of their serum folate concentrations because it is a short-term indicator of dietary folate intake: the 'low folate group' (serum folate <9 ng/ml) and the 'high folate group' (serum folate ⩾9 ng/ml). Comparison between the two groups was performed using an unpaired *t*-test for nutrient intakes and Mann–Whitney's *U* test for intakes of food groups because of their skewed distributions. Correlations across selected blood biomarkers were analyzed by Spearman's correlation coefficients. To diminish the influence of the absolute amount of food intake on the selected nutrients and also to obtain indicators of the nutritional quality of daily food patterns, nutrient densities expressed per 1000 kcal were used for further analyses.

Results

General characteristics

The general characteristics of the subjects are presented in Table 1. The age of the subjects ($n=70$) ranged from 17 to 41 years. The median point of the folate concentration

Table 1 Characteristics of study subjects

Variables	n = 70	
	Mean (s.d.)	*Range*
General characteristics		
Age	29.9 (5.0)	17–41
Weeks of gestation at survey	10.6 (1.8)	7–15
Primipara (%)	81.4	—
Height (cm)	158.5 (5.0)	147–168
Prepregnancy weight (kg)	52.2 (9.1)	38–80
Current weight (kg)	53 (8.8)	38–85
Prepregnancy BMI (kg/m^2)	20.8 (3.9)	16.1–34.7
Current BMI	21.1 (3.6)	16.3–34.9
Vitamin[a] or mineral supplement use (%)	11.4	—
Smoking (%)	18.6	—
Drinking (%)	2.9	—
Blood biomarkers		
Serum folate (ng/ml)	10.3 (5.0)	5.5–33.0
RBC folate (ng/ml)[b]	519 (231)	165–1104
Plasma homocysteine (nmol/ml)	5.2 (1.4)	2.7–10.7
Plasma vitamin B_{12} (pg/ml)	423 (134)	230–930
Hemoglobin (g/dl)	12.6 (0.9)	10.2–14.3
Hematocrit (%)	36.3 (2.6)	29.9–41.5
Serum ferritin (ng/Ml)	42.4 (37.2)	4.6–210

[a]Except folate.
[b]$n=50$.

Table 2 Demographic and anthropometric characteristics in groups defined by serum folate concentration

Variables	*Serum folate*				*P-values*
	<9 ng/ml (n = 34)		*⩾9 ng/ml (n = 36)*		
	Mean (s.d.)	*Range*	*Mean (s.d.)*	*Range*	
General characteristics					
Age[a]	30.2 (5.4)	17–41	29.4 (4.0)	17–37	0.506
Weeks of gestation at survey[a]	10.8 (2.1)	7–15	10.4 (1.3)	8–13	0.41
Primipara (%)[b]	71	—	92	—	<0.0001
Height (cm)[a]	158.6 (4.6)	148–168	158.5 (5.0)	147–167	0.812
Prepregnancy body weight (kg)[a]	52.2 (8.9)	40–80	52.1 (8.3)	38–76	0.949
Current body weight (kg)[a]	53.9 (9.2)	42.5–85	52.0 (6.5)	38–66	0.359
Prepregnancy BMI (kg/m^2)[a]	20.8 (3.6)	16.2–32.9	20.7	16.1–34.7	0.891
Current BMI[a]	21.4 (3.7)	17–34.9	16.1–34.7	16.3–30.1	0.435
Vitamin[c] or mineral supplement use (%)[b]	8.8	—	8.3	—	0.151
Smoking (%)[b]	20.6	—	16.7	—	0.327
Drinking (%)[b]	2.9	—	2.8	—	0.967
Blood biomarkers					
Serum folate (ng/ml)	7.5 (0.9)	5.5–8.9	13.1 (5.3)	9–33	0.0001
RBC folate[d] (ng/ml)	429 (154)	210–978	605 (263)	165–1104	0.01
Plasma homocysteine (nmol/ml)	5.6 (1.5)	3.7–10.7	4.9 (1.3)	2.7–7.8	0.052
Plasma vitamin B_{12} (pg/ml)	405 (116)	230–690	432 (152)	250–940	0.410
Hemoglobin (g/dl)	12.4 (1.0)	10.2–14.3	12.8 (0.7)	10.9–14.2	0.083
Hematocrit (%)	35.6 (2.7)	29.9–39.6	37.0 (2.3)	31.8–41.5	0.03
Serum ferrtin (ng/ml)	39.0 (28.2)	6.8–120	45.1 (37.8)	6.1–210	0.449

[a]Unpaired *t*-test.
[b]χ^2-test.
[c]Except folate.
[d]<9 ng/ml ($n=24$), ⩾9 ng/ml ($n=26$).

(9 ng/ml) subdivided the subjects into the 'low folate group' ($n=34$) and the 'high folate group' ($n=36$).

The demographic and anthropometric characteristics of the two groups are presented in Table 2. Age, week of gestation, height and body mass index (BMI) did not differ significantly between the two groups. The number of primipara was significantly higher in the higher group than that in the lower group. The number of users of other vitamin supplements was not different in the two groups, although the number of smokers was marginally higher in the lower group.

Biological markers

Blood biological markers of all study subjects are shown in Table 1.

Mean levels of serum and RBC folate concentration were 10.3ng/ml ($n=70$) and 519ng/ml ($n=50$), respectively. The distribution of serum folate concentration is shown in Figure 1. Serum folate was <6 ng/ml in 4.3% of subjects, and $\geqslant 13$ ng/ml in 14.3% of subjects. Although none of the subjects took any folate supplements, the mean serum and RBC folate levels were higher than in published reports in other countries (Cuskelly *et al.*, 1996; Brown *et al.*, 1997).

When the selected biological markers were compared between the two groups, the group with higher serum folate concentrations showed higher RBC folate concentrations ($P=0.01$) and a higher hematocrit ($P=0.03$) than the group with lower serum folate concentrations (Table 2). Homocysteine levels, the other marker affecting blood folate concentration, were marginally higher in the group with lower serum folate concentrations.

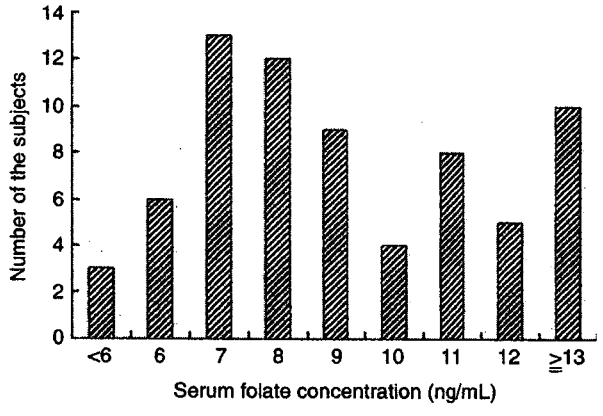

Figure 1 Distribution of serum folate concentration in all subjects ($n=70$).

Correlation coefficients across blood biomarkers

Correlation coefficients across blood biomarkers are shown in Table 3. Serum folate was positively correlated with RBC folate, plasma B_{12}, hemoglobin, albumin and hematocrit, and inversely correlated with plasma homocysteine. Although RBC folate concentration was inversely correlated with plasma homocysteine, no significant correlation was observed between other biomarkers.

Dietary intake

Average nutrient intakes per day in all subjects from 3-day diet records are shown in Table 4. When comparing with the newly revised dietary recommendation for pregnant women in Japan, intakes of calcium, copper, vitamin A, B_2, B_{12} and vitamin C seem to be relatively adequate although a proportion of each distribution did not reach the level of estimated average requirements. Average intakes of folate, iron, zinc, vitamin D, B_1 and B_6 were lower than the recommended values. The distribution of folate intake in the two groups classified according to serum folate concentration is shown in Figure 2. More than 70% of subjects had a folate intake below 200 μg/day.

Energy-adjusted nutrient intakes (nutrient per 1000 kcal) in the two groups are shown in Table 5. Folate, calcium and fiber intakes per 1000 kcal were significantly greater in the high folate group than in the low folate group.

We also analyzed the mean daily consumption of foods groups (Table 6). In some food groups the intake levels differed significantly between the low folate group and the high folate group; the subjects in the high folate group consumed more spinach, fruit, and fruits juice, and fewer meats, oils and fats than the low folate group.

Discussion

Many recent studies have indicated that folate nutrient status is very important for women in early pregnancy because folic acid reduces the risk of NTD (Berry *et al.*, 1999; Werler *et al.*, 1999; Ray *et al.*, 2002). Many countries recommend a high-folate diet and folic acid supplements for pregnant women and women wishing to become pregnant (Green, 2002). However, the folate nutritional

Table 3 Correlation coefficients between blood biomarkers in all subjects

	Serum folate	*RBC folate*	*Plasma homocystein*	*Plasma vitamin B_{12}*	*Hemoglobin*	*Albumin*	*Hematocrit*	*Serum ferritin*
Serum folate	1.000	0.464**	−0.420****	0.300*	0.308*	0.452****	0.358***	−0.0006
RBC folate		1.000	−0.336*	0.128	0.105	0.076	0.067	−0.200

All data are log-transformed.
*$P<0.05$, **$P<0.01$, ***$P<0.005$; ****$P<0.001$.

Table 4 Nutrient intake/day from natural food sources in study subjects

Variables	*Japanese recommendation for pregnant women in first trimester*		*All subjects (n = 70)*	
	18–29 years old	*30–49 years old*	*Mean (s.d.)*	*Range*
Energy (kcal)	2100	2050	1782 (489)	1007–3690
Total protein (% of energy)	<20	<20	14.1 (9.5)	9.5–22.1
Total fat (% of energy)	20–30	20–30	28.7 (6.3)	12.6–42.8
Cholesterol (mg)	<600	<600	309 (157)	56–885
Calcium (mg)	700	600	601 (325)	93–2013
Iron (mg)	19.5	19.5	7.0 (4.1)	1.0–33.2
Copper (mg)	0.8	0.8	1.04 (0.36)	0.26–2.79
Zinc (mg)	10	10	7.4 (2.4)	1.9–18.4
Vitamin A (μg/RE)	670	670	982 (839)	110–4022
Vitamin D (μg)	7.5	7.5	5.7 (6.0)	0.5–40.8
Vtamin B_1 (mg)	1.1	1.1	1.06 (1.53)	0.21–13.37
Vtamin B_2 (mg)	1.2	1.2	1.94 (5.06)	0.30–44.18
Vitamin B_6 (mg)	2.0	2.0	1.6 (3.9)	0.3–34.2
Vtamin B_{12} (μg)	2.8	2.8	6.2 (5.5)	0.5–31.1
folate (μg)	440	440	289 (151)	68–1151
Vtamin C (mg)	110	110	143 (202)	11–1249
Fiber (g)	21	20	12.9 (5.9)	1.9–46.3
Sodium chloride equivalent (g)	<8	<8	10.5 (4.2)	1.6–27.7

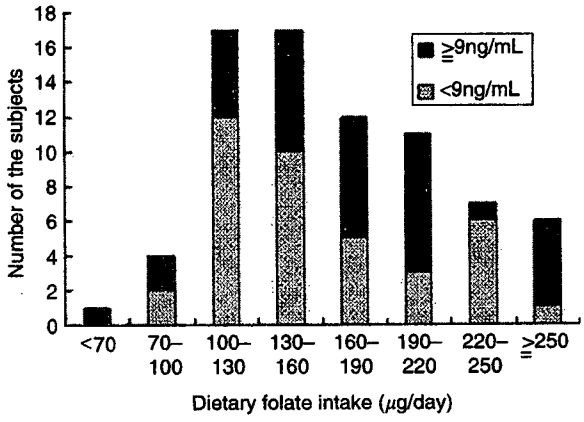

Figure 2 Distribution of RBC folate concentration in groups defined by serum folate concentration. Gray bar: low folate group (<9 ng/ml), black bar: high folate group (≥9 ng/ml).

profile of Japanese pregnant women has not been fully investigated because there has been little awareness of this in Japan, and folate has only recently been added to the Dietary Reference Intakes for Japanese and the Standard Food Composition Table. Specifically, there has been no study of folate intake and blood folate biomarkers in woman in early pregnancy in Japan. Folate is also important to achieve normal birth weight because it is reported that a low intake of folate in pregnant women is associated with low birth weight (Rao *et al.*, 2001). Therefore, it is important to study folate nutrition in pregnant women in Japan.

The recommended dietary allowance (RDA) of folate in early pregnancy for prevention of NTD is 440 μg/day in the Dietary Reference Intakes for Japanese, 2005 (Ministry of Health, Labour, and Welfare, Japan, 2005). Mean folate intake/day in all subjects was 289 μg/day in the present study. Only 8.6% of subjects had a folate intake above 250 μg/day, and folate intake was below the RDA in 94 % of subjects. The National Nutrition Survey in Japan showed that the mean folate intake of Japanese women aged 20–50 years was 200–300 μg/day (Ministry of Health, Labour, and Welfare, Japan, 2005). Folate intake was not sufficient in pregnant Japanese women in the first trimester. However, they showed a higher mean serum folate concentration (10.3 ng/ml) than reported in other countries. For example, The US data from NHANES III 1988–1994 showed mean serum and RBC folate levels, 4.8 and 159.9 ng/ml, respectively for reproductive age but nonpregnant women, which were observed before the mandated folate fortification in this country (CDC, 2002). Even in low intake groups in the present study, most subjects had serum folate concentrations above 7 ng/ml. Hirooka (2001) reported that the mean serum folate concentration in nonpregnant Japanese women aged 21–22 years was 17.9 nmol/l (7.4 ng/ml). The level is lower than in the present study. All our subjects were above the lower border of the normal serum folate range, 3.0 ng/ml (Jacques *et al* 1999). On the other hand, Kondo *et al* reported that Japanese pregnant women revealed serum folate of 11.9 ng/ml, which is the average of all trimester. As our present data is only a first trimester, it is need to investigate serum folate of pregnant women in the second and third trimester. Many trials have reported that folic acid supplements or a high folate diet increased serum folate levels compared with baseline (Cuskelly *et al.*, 1996; Brown *et al.*, 1997; Jacques *et al.*, 1999). However, serum folate concentrations of our subjects were same level with reported data of folic acid supplements user. It was very interesting because users of folic acid supplements were not

Table 5 Energy-adjusted nutrient intake/day from natural food sources in groups defined by serum folate concentration

Variables	*Serum folate*				*P-value*
	<9 ng/ml (n=34)		*≥9 ng/ml (n=36)*		
	Mean (s.d.)	*Range*	*Mean (s.d.)*	*Range*	
Energy (kcal)	1856 (424)	1042–2887	1734 (535)	1007–3690	0.300
Total protein (% of energy)	14.0 (1.9)	9.9–17.9	14.3 (2.6)	11.1–22.1	0.653
Total fat (% of energy)	29.9 (6.7)	12.6–42.8	27.7 (5.8)	17.9–41.1	0.151
Cholesterol (mg/1000 kcal)	180 (62)	44–345	167 (74)	49–726	0.433
Calcium (mg/1000 kcal)	293 (105)	158–540	374 (169)	92–953	0.018
Iron (mg/1000 kcal)	3.7 (0.8)	2.7–6.3	4.21(1.84)	2.1–11.4	0.115
Copper (mg/1000 kcal)	0.57 (0.11)	0.40–0.89	0.60 (0.12)	0.39–0.84	0.308
Zinc (mg/1000 kcal)	4.1 (0.7)	3.1–6.0	4.29 (0.79)	2.57–6.39	0.327
Vitamin A (μg/RE/1000 kcal)	533 (479)	123–2643	570 (354)	173–1805	0.717
Vitamin D (μg/1000 kcal)	3.1 (2.8)	0.6–9.7	3.5 (5.0)	0.34–29.2	0.676
Vitamin B_1 (mg/1000 kcal)	0.52 (0.31)	0.26–1.94	0.68 (1.12)	0.32–7.15	0.417
Vitamin B_2 (mg/1000 kcal)	0.71 (0.36)	0.39–2.24	1.50 (3.89)	0.4–23.6	0.235
Vitamin B_6 (mg/1000 kcal)	0.61 (0.36)	0.34–2.26	1.2 (2.98)	0.4–18.3	0.29
Vitamin B_{12} (μg/1000 kcal)	3.3 (2.25)	0.86–8.59	3.6 (3.2)	0.3–16.2	0.622
folate (μg/1000 kcal)	144 (49)	70–314	182 (76)	62–392	0.013
Vitamin C (mg/1000 kcal)	62 (108)	10–661	112 (142)	13–668	0.105
Fiber (g/1000 kcal)	6.7 (1.6)	3.0–9.7	7.8 (2.7)	3.9–15.8	0.036
Sodium chloride equivalent (g/1000 kcal)	4.3 (1.4)	1.8–8.1	4.2 (1.8)	1.8–11	0.727

Table 6 Mean intakes (g/day) of main food groups in groups defined by serum folate concentration

Variables	*Serum folate*		*P-value*
	<9 ng/ml (n=34)	*≥9 ng/ml (n=36)*	
	Mean (s.d.)	*Mean (s.d.)*	
Grain	534.5 (175.2)	501.5 (268.5)	0.259
Rice	229.8 (89.5)	206.0 (136.3)	0.155
Breads	53.1 (37.0)	49.8 (42.2)	0.819
Noodles, Pasta	88.8 (70.3)	84.9 (96.8)	0.437
Nuts, Seed	2.6 (6.0)	1.8 (3.1)	0.542
Potatoes	46.8 (44.5)	52.2 (78.0)	0.778
Sugar	4.0 (5.0)	4.9 (5.3)	0.513
Confectionaries	45.4 (41.9)	49.5 (59.6)	0.938
Oil, Fats	16.2 (8.5)	11.9 (6.0)	0.037
Meats	82.8 (41.6)	58.7 (42.6)	0.013
Fish/shell fish	44.0 (30.3)	43.8 (35.4)	0.710
Eggs	20.2 (25.9)	30.1(22.9)	0.635
Milk	78.0 (99.3)	165.4 (178.7)	0.090
Other milk products	96.9 (109.3)	72.1 (72.5)	0.250
Cheeses	4.8 (5.7)	4.8 (7.8)	0.744
Soybean, soybean products	37.5 (39.4)	36.7 (52.2)	0.543
Mushrooms	9.3 (12.0)	12.4 (18.2)	0.754
Colored vegetables	76.6 (55.2)	104.0 (81.7)	0.086
Carots	10.8 (14.4)	14.6 (18.7)	0.614
Tomatoes	24.6 (40.7)	33.7 (36.7)	0.108
Spinach	8.4 (11.3)	18.9 (31.0)	0.043
Pepper	5.9 (7.4)	2.4 (4.7)	0.058
Other vegetables	104.9 (50.3)	120.2 (113.8)	0.947
Fruits	136.7 (135.6)	239.7 (146.6)	0.001
Citrus fruits	23.4 (28.5)	43.8 (58.9)	0.110
Apples	29.8 (40.1)	26.7 (54.4)	0.621
Bananas	16.6 (21.4)	19.4 (39.5)	0.562
Fruits juice	56.8 (74.5)	94.2 (104.4)	0.040
Coffee, Cocoa	69.6 (91.0)	41.5 (76.8)	0.338
Tea	183.9 (254.6)	215.6 (187.1)	0.324
Alcohol beverages	13.3 (37.0)	4.9 (13.8)	0.174

included, and none of the participants ate foods fortified with folate.

We analyzed nutrient intake and consumption of food groups in the two groups defined by serum folate concentration: the high folate (serum folate ≥9 ng/ml) group and the low folate (serum folate <9 ng/ml) group. The high folate group showed higher energy-adjusted intakes of folate, calcium and fiber compared with the low folate group. Many studies have reported that folic acid is directly correlated with blood folate concentration, and is useful for the prevention of NTD (Cuskelly *et al.*, 1996; Brown *et al.*, 1997; Berry *et al.*, 1999; Jacques *et al.*, 1999; Werler *et al.*, 1999; Ray *et al.*, 2002). As dietary folate contains a polyglutamate chain, the bioavailability of folate varies widely with different foods and cooking styles. Utilization of polyglutamate is affected by many factors, such as

intestinal matrix effects or pH. Therefore, the bioavailability of natural food folate is thought to be 20–75% that of folic acid (Gregory, 2001; van den Berg *et al.*, 2002; Melse-Boonstra *et al.*, 2002; Kim *et al.*, 2004). The only sources of folate in the subjects of the present study were natural foods. Therefore, it is very important to clarify the association between the intake of natural food folate in Japanese food and blood folate concentrations. Some researchers reported that high folate diets, fresh berries, citrus fruit, and vegetables significantly increased blood folate concentrations or significantly decreased plasma total homocysteine (Brouwer *et al.*, 1999; Koebnick *et al.*, 2001; Silaste *et al.*, 2003). We compared the mean consumption of food groups in two groups classified by serum folate concentration. The intakes of colored vegetables, spinach and fruits were significantly greater in the high folate group than in the low folate group, while the intake of meats, oils and fats was greater in the low folate group than in the high folate group. Although plasma homocysteine levels were inversely correlated with serum folate and RBC folate levels, it did not differ significantly between the two groups. Serum folate levels were positively correlated with RBC folate and plasma vitamin B_{12} levels. Serum folate also correlated significantly with other blood markers, hemoglobin, albumin, hematocrit and serum ferritin. These findings suggested that the eating pattern in pregnant Japanese women, which maintained a sufficient serum folate concentration, may also support a healthy pregnancy. The National Nutrition Survey, Japan (Takimoto *et al.*, 2003) found that pregnant Japanese women were aware of the importance of adopting healthy behaviors (smoking less, drinking less, etc.) and taking more milk, fruit or colored vegetables during pregnancy. In the present study, the typical dietary pattern of women in early pregnancy, especially in the high folate group, included a high intake of vegetable, fruits, milk, soy products and fish, and a low intake of oil and fat, and meat.

Levels of vitamin B_{12}, which supports folate metabolism, and calcium were adequate in our subjects. The main dietary source of calcium in Japan is milk. Milk contains folate-binding protein (FBP). As it has been reported that FBP may increase the bioavailability of dietary folate (Jones and Nixon, 2002; Jones *et al.*, 2003), adequate milk consumption may be partly responsible for higher serum folate concentrations in pregnant Japanese women. RBC folate concentrations varied widely between subjects, especially in the high folate group. This suggests that RBC folate may be preferable to serum or plasma folate for the prediction of NTD risk (Bunduki *et al.*, 1995; Daly *et al.*, 1995). Brown *et al* showed that a folate concentration of $\geqslant$400 ng/ml in early pregnancy decreased the risk of NTD (Brown *et al.*, 1997). In the present study, most of the subjects showed a RBC folate concentration $\geqslant$400 ng/ml, although a few of the subjects had a RBC folate concentration $<$200 ng/ml, even in the high serum folate group. It is therefore possible that preconception folate nutrition may be insufficient in some subjects, because RBC folate concentration is a longer-term index of folate nutrition than serum folate. However, RBC data in the present study were preliminary ($n=50$), and further studies are needed.

Our study is the first to describe folate nutrition in early pregnancy in Japan. Further study is needed using longitudinal studies from preconception to early pregnancy to determine the appropriate intake of folate in pregnant Japanese women in the first trimester.

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Restricting weight gain during pregnancy in Japan: A controversial factor in reducing perinatal complications

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Abstract

Objective: To evaluate the effectiveness of restricting weight gain during pregnancy to reduce perinatal complications.
Study design: The study was conducted in the Tokyo metropolitan area, and reviewed 3071 mothers and their infants born from singleton pregnancies retrospectively. To examine the influence of increased maternal weight gain on perinatal complications, we performed five-category stratification for weight gain: less than 8.0, 8.0–10.0, 10.1–12.0, 12.1–14.0 and over 14.0 kg.
Results: Total weight gains less than 8.0 kg significantly increased the risk of low birth weight (LBW) and small for gestational age (SGA) infants (OR = 2.19, 95% CI; 1.36–3.52, OR = 1.76, 95% CI; 1.23–2.51) and total weight gain over 14.0 kg significantly increased the risk of large for gestational age (LGA) infants and pregnancy induced hypertension (PIH) (OR = 3.06, 95% CI; 1.88–4.98, OR = 2.87, 95% CI; 1.86–4.42, respectively), compared with women with weight gain of 10.1–12.0 kg. The groups with weight gains of 8.0–10.0 kg and 12.1–14.0 kg did not show adverse perinatal outcomes, including gestational diabetes (GDM), cesarean delivery, postpartum hemorrhage and laceration, significantly different from the 10.1 to 12.0 kg gain group.
Conclusion: Strict restriction of weight gain during pregnancy is not effective in reducing perinatal complications.
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Keywords: Maternal weight gain; Prepregnancy body mass index (BMI); Perinatal complications

1. Introduction

Greater maternal weight gains were believed to increase the risks of gestational diabetes (GDM), pregnancy induced hypertension (PIH), eclampsia, cesarean delivery, macrosomia and prolonged difficult labor, postpartum hemorrhage and fetal trauma [1–5]. However, weight gain restriction had adverse birth outcomes. In 1990, the Institute of Medicine (IOM) in the United States revised the guidelines for weight gain during pregnancy, which recommend an optimal weight gain range for women based on their prepregnancy body mass index (BMI) because insufficient weight gain could contribute to premature births and to low birth weight (LBW) term infants [6]. In addition, Thorsdottir et al. [7] suggested that in an American population studied, unnecessary weight gain had no beneficial effect on health and inferred that low weight gain should also be avoided to optimize birth outcome. Restricted weight gain may even have negative consequences for women's well-being in the form of stress and worries optimal weight range, and it may consequently restrict optimal birth weight.

The Japan Society of Obstetrics and Gynecology (JSOG) issued guidelines for optimal weight gain during pregnancy, which are based on prepregnancy BMI, in order to prevent the risk of PIH, in 1997 [8]; recommended weight gains are

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10–12 kg for women of BMI < 18.0, 7–10 kg for women of 18.0 ≦ BMI ≦ 24.0, and 5–7 kg for women of BMI > 24.0, respectively. Although nutritional education or counseling on weight gain restriction has been undertaken in many hospitals or clinics in Japan following this guideline, very few studies were undertaken to assess the adverse effects of excessive maternal weight gain on pregnancy outcome. In addition, it is still controversial whether different cutoff values in various studies might offer results as good as, or better than, those recommended by the JSOG. At present, no upper or lower limit of maternal weight gain is provided to reduce the risk of perinatal complications.

Thus, it is still unclear which weight gain range has the stronger effect in the effort to avoid complications. Studies that report maternal and fetal health outcomes over the entire spectrum of weight change might help to clarify whether there are wider weight gain ranges for women. The purpose of our study was to evaluate the effectiveness of restricting weight gain during pregnancy in reducing perinatal complications.

2. Materials and methods

2.1. Subjects

In this retrospective study, we analyzed data on the 3071 mothers and their infants born at 37–42 weeks of gestation from singleton pregnancies during the years 2002 and 2003 in Nagai Clinic, Saitama, and Sagamihara Kyoudou Hospital, Kanagawa, which are located in Japan's Tokyo metropolitan area. Multiple pregnancies, stillborns and malformed fetuses were excluded from the study. Subjects were classified according to prepregnancy BMI (kg/m^2) into underweight (BMI < 18.5), normal (18.5 < BMI ≦ 25.0), and overweight (BMI > 25.0) groups, following the definitions of the Japan Society for the Study of Obesity [9], because Asian countries have a lower prevalence of obesity, despite their high rates of obesity-related diseases. This criterion differs from that of the National Institute of Health [10].

2.2. Anthropometric measurements and data collection

Other demographic data including age, parity and medical history were obtained from prenatal records. After delivery, the newborn anthropometric characteristics were measured and recorded; birth weight, length, head and chest circumference. Ponderal index was calculated as birth weight (g) divided by length (cm). Low birth weight (LBW: birth weight less than 2500 g), macrosomia (more than 4000 g), small for gestational age (SGA: birth weight below the 10th percentile for gestational age) and large for gestational age (LGA: birth weight above the 90th percentile for gestational age) which were classified by Nishida et al. [11] were also defined as neonatal outcomes. PIH was defined by World Health Organization criteria as a blood pressure over 140/90 mmHg [12]. GDM was defined by the JSOG criteria and diagnosed on the basis of a 75 g oral glucose tolerance test if the following diagnostic criteria are used in two or three categories: a fasting blood glucose of more than 100 mg/dl, a plasma glucose levels 60 min after loading of more than 180 mg/dl, and levels of more than 150 mg/dl 120 min after loading [13]. Postpartum heamorrhage was defined as excessive bleeding (more than 500 ml) due to failure of the myometrium to contract at the placental site.

In this study, total pregnancy weight gain was defined as the difference between measured weight at the last prenatal visit closest to delivery and self-reported prepregnancy weight. In the present study, the 25th, 50th, 75th and 90th percentiles for maternal weight gain are 7.4, 9.6, 11.9 and 14.2 kg, respectively. To examine the influence of increased maternal weight gain on perinatal complications, we stratified the data into five categories for weight gain based on these percentile values, because these values may be useful to clinicians providing optimal weight gain as prenatal care: less than 8.0, 8.0–10.0, 10.1–12.0, 12.1–14.0 and over 14.0 kg.

2.3. Statistical analysis

Differences in continuous variables by prepregnancy BMI category were determined by the Mann–Whitney–Wilcoxon test for non-normally distributed data, or ANOVA with Tukey's adjustment for normally distributed data. Differences in proportion of categorical variables were compared using χ^2-test. Multivariate logistic regression was used to evaluate the association between maternal total weight gain and perinatal complications. Interaction analysis between prepregnancy BMI categories and maternal weight gain during pregnancy was firstly carried out to ascertain the effect on perinatal outcomes before logistic regression was performed. We confirmed that the interaction was not significant. Adjusted odds ratio (OR) and 95% confidence intervals (CI) were estimated. Differences were considered to be significant at $p < 0.05$. Statistical analysis was carried out with SPSS for Windows, version 12.0 (SPSS Inc., Chicago III, USA).

3. Results

The investigation was undertaken using data from 3071 mothers who gave birth in selected hospitals in the metropolitan area of Tokyo between January 2002 and December 2003. Table 1 presents the maternal and neonatal demographic characteristics. Out of 3071 deliveries, 16.1% were underweight (BMI < 18.5 kg/m^2; $n = 493$, minimum 14.8), 74.9% were normal (18.5 ≦ BMI ≦ 25.0 kg/m^2; $n = 2301$) and 9.0% were obesity (BMI > 25.0 kg/m^2;

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Table 1
Demographic characteristics

	All category, $n = 3071$	BMI category (kg/m^2)			p-Value
		Underweight, $n = 493$ (16.1%)	Normal, $n = 2301$ (74.9%)	Obesity, $n = 277$ (9.0%)	
Mother					
Age (year)	29.4 ± 4.3	28.6 ± 4.3 bc	29.4 ± 4.3 ac	30.7 ± 4.2 ab	<0.001
Over 35 years old (%)	11.3	8.1	11.4	16.2	<0.01
Under 20 years old (%)	1.3	1.0	1.5	0.4	NS
Height (cm)	158.2 ± 5.1	158.7 ± 5.1	158.2 ± 5.1	157.8 ± 5.5	NS
Weight gain (kg)	9.6 ± 3.7	10.5 ± 3.3 bc	9.8 ± 3.4 ac	6.6 ± 4.8 ab	<0.001
Prepregnancy BMI (kg/m^2)	21.0 ± 3.0	17.6 ± 0.7	20.9 ± 1.6	28.1 ± 2.9	<0.001
Primiparous (%)	51.6	58	51.5	41.2	<0.001
Smoking (%)	15.8	16.8	16.8	15.8	NS
Infant					
Gestational week (w)	39.5 ± 1.0	39.4 ± 1.0	39.5 ± 1.0	39.5 ± 1.0	NS
Birth weight (g)	3061.8 ± 353.3	2993.0 ± 343.1 bc	3065.8 ± 348.7 ac	3150.5 ± 385.7 ab	<0.001
Birth length (cm)	49.0 ± 1.7	48.7 ± 1.7 bc	49.0 ± 1.7 ac	49.3 ± 1.9 ab	<0.001
Head circumstance (cm)	33.0 ± 1.2	33.0 ± 1.2	33.0 ± 1.2	33.2 ± 1.3	NS
Chest circumstance (cm)	31.6 ± 1.5	31.4 ± 1.4 bc	31.7 ± 1.5 a	31.8 ± 1.6 a	<0.05
Ponderal index (kg/m^3)	26.0 ± 2.4	25.8 ± 2.0 c	26.0 ± 2.5	26.2 ± 2.0 a	<0.05
Placenta weight (g)	579.3 ± 102.4	553.6 ± 92.3 bc	580.1 ± 101.6 ac	618.5 ± 101.6 ab	<0.001

BMI: body mass index, NS: nonsignificant; BMI categories (underweight < 18.5, normal 18.5–25.0, obesity > 25.0). Values are presented as mean ± S.D. or %; letters show the values that are significantly different ($p < 0.05$, Tukey's test or Mann–Whitney test).

$n = 277$, maximum 43.1). The average maternal age was 29.4 ± 4.3.

The mean weight gains during pregnancy for the underweight and normal women were 10.5 kg (range −0.8 to +21.5), 9.8 kg (range −1.7 to +24.0), respectively. For obese women, the median weight gain was 6.9 kg (range −9.6 to +24.0). There were significant differences among the three groups ($p < 0.001$). Smoking prevalence was 15.8% in all categories with no significant difference among the three groups. Although the numbers of gestational weeks when classified by prepregnancy BMI were not significantly different, the mean birth weight in underweight women was lower than those of the normal and obese women (2993.0 ± 343.1 g, 3065.8 ± 348.7 g, 3150.5 ± 385.7 g, respectively, $p < 0.001$). In addition, the mean length and chest circumference were significantly lower ($p < 0.001$, $p < 0.05$, respectively) than those of the normal and obese women.

Table 2 shows the results of pregnancy outcome classified by prepregnancy BMI. The proportion of LBW infants was higher in underweight women than in normal and obese women (7.5%, 4.6%, 4.7%, respectively, $p = 0.03$). The proportion of SGA infants was higher in underweight women than in normal and obese women, but the differences were not significant (11.0%, 8.0%, 8.7%, respectively, $p = 0.1$). PIH prevalence was 8.5%, where the prevalence of underweight, normal and obese women was 4.1%, 7.1% and 27.4%, respectively ($p < 0.001$). The PIH prevalence in obese women was 6 times that in the underweight women. The proportion of cesarean sections was also higher in the obese women than in underweight and normal women (9.7%, 3.4%, 3.8%, respectively, $p < 0.001$).

Table 3 shows the perinatal outcomes by prepregnancy BMI category. In underweight women, the odds ratio of LBW and SGA were significantly increased by 1.7 (95% CI; 1.15–2.51), 1.45 (95% CI; 1.13–2.00), respectively,

Table 2
Frequencies of perinatal outcomes

	All category, $n = 3071$	BMI category (kg/m^2)			p-Value
		Underweight, $n = 493$ (16.1%)	Normal, $n = 2301$ (74.9%)	Obesity, $n = 277$ (9.0%)	
LBW	155 (5.0)	37 (7.5)	105 (4.6)	13 (4.7)	0.03
SGA	262 (8.5)	54 (11.0)	184 (8.0)	24 (8.7)	0.10
LGA	170 (5.5)	16 (3.2)	127 (5.5)	27 (9.7)	<0.001
Macrosomia	20 (0.7)	1 (0.2)	15 (0.7)	4 (1.4)	0.12
PIH	260 (8.5)	20 (4.1)	164 (7.1)	76 (27.4)	<0.001
GDM	138 (4.5)	28 (5.7)	97 (4.2)	13 (4.7)	0.36
C/S	132 (4.3)	17 (3.4)	88 (3.8)	27 (9.7)	<0.001
Postpartum hemorrhage	90 (2.9)	13 (2.6)	66 (2.9)	11 (4.0)	0.54
Laceration	588 (19.1)	105 (21.3)	422 (18.3)	61 (22.0)	0.14

Values are presented as n (%); BMI categories (underweight < 18.5, normal, 18.5–25.0, and obesity > 25.0). p-Value based on χ^2-test for percent. LBW: low birth weight, SGA: small for gestational age, LGA: large for gestational age. PIH: pregnancy induced hypertension, GDM: gestational diabetes, C/S: cesarean section.

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Table 3
Adjusted odds ratios (OR) of perinatal outcomes by prepregnancy BMI

	BMI category (kg/m^2)		
	Underweight, OR (95% CI)	Normal, OR	Obesity, OR (95% CI)
LBW	1.7 (1.15–2.51)	1.0	1.03 (0.57–1.86)
SGA	1.45 (1.13–2.00)	1.0	1.04 (0.67–1.64)
LGA	0.56 (0.33–0.96)	1.0	1.91 (1.23–2.96)
Macrosomia	0.3 (0.04–2.31)	1.0	2.31 (0.75–7.11)
PIH	0.55 (0.34–0.89)	1.0	4.89 (3.58–6.68)
GDM	1.37 (0.89–2.11)	1.0	1.11 (0.61–2.02)
C/S	0.89 (0.52–1.51)	1.0	2.72 (1.72–4.31)
Postpartum hemorrhage	0.91 (0.50–1.67)	1.0	1.41 (0.73–2.72)
Laceration	1.24 (0.98–1.58)	1.0	1.19 (0.88–1.62)

CI: confidence interval; BMI categories (underweight < 18.5, normal, 18.5–25.0, obesity > 25.0). LBW: low birth weight, SGA: small for gestational age, and LGA: large for gestational age. PIH: pregnancy induced hypertension, GDM: gestational diabetes, C/S: cesarean section. Adjusted for maternal age, parity and maternal weight gain.

compared with the normal. On the other hand, in the obese women, the odds ratios of LGA, PIH and cesarean section were increased significantly, by 1.91 (95% CI; 1.23–2.96), 4.89 (95% CI; 3.58–6.68), 2.72 (95% CI; 1.72–4.31), respectively, compared with the normal. No increase in odds ratio was observed for macrosomia, GDM, postpartum hemorrhage and laceration in prepregnancy BMI categories.

Table 4 shows the distribution of perinatal complications within maternal weight gain categories. Women with total weight gain less than 8 kg had significantly increased risk of LBW and SGA infants (OR = 2.19, 95% CI; 1.36–3.52, OR = 1.76, 95% CI; 1.23–2.51, respectively). On the other hand, women with total weight gains over 14 kg showed a significantly increased the risk of LGA infants and PIH (OR = 3.06, 95% CI; 1.88–4.98, OR = 2.87, 95% CI; 1.86–4.42, respectively). There was no statistically significant difference in the incidence of GDM, cesarean delivery, macrosomia, postpartum hemorrhage and laceration between the weight gain categories. Total weight gain with 8–10 and 12.1–14 kg groups did not show any significant influence on the other perinatal outcomes.

4. Comment

This is the first epidemiological study in which we have examined the ranges of maternal weight gain in 2 kg intervals ranging from less than 8 kg to more than 14 kg, and whether they affect or protect against the perinatal complications as classified by prepregnancy BMI among Japanese women. In order to define where in the range of maternal weight gain the risk increases, the women were divided into five categories as follows: under 8.0, 8.0–10.0, 10.1–12.0, 12.1–14.0, over 14.0 kg. This study may contribute to analysis of the factors causing recent trends of increases in the proportion of LBW infants and of decreases in the average birth weight in Japan, because the birth weights have gradually declined from 3.16 to 3.07 kg for boys and 3.08 to 2.99 kg for girls from 1990 to 2000, and the prevalence rates of LBW infants have also increased 5.7–7.8 for boys and 7.0–9.5 for girls, during the same periods [14]. In our results, the total incidence of LGA infant was only 5.5%, which was well below 10%. An analysis of the major factors causing recent trends is important in order to reduce the risk of perinatal complications and contribute to

Table 4
Adjusted odds ratio (OR) of perinatal outcomes by weight gain

	Maternal weight gain (kg)									
	<8.0, n = 925 (30.1%)		8.0–10.0, n = 747 (24.3%)		10.1–12.0, n = 635 (20.7%)		12.1–14.0, n = 414 (13.5%)		>14.0, n = 350 (11.4%)	
	n (%)	95% CI	n (%)	OR (95% CI)	n (%)	OR	n (%)	OR (95% CI)	n (%)	OR (95% CI)
LBW	68 (7.4)	2.19 (1.36–3.52)	38 (5.1)	1.32 (0.79–2.21)	25 (3.9)	1.0	14 (3.4)	0.84 (0.43–1.63)	10 (2.9)	0.71(0.37–1.50)
SGA	110 (11.9)	1.76 (1.23–2.51)	64 (8.6)	1.08 (0.73–1.59)	51 (8.0)	1.0	21 (5.1)	0.59 (0.35–0.99)	16 (4.6)	0.54 (0.30–0.99)
LGA	41 (4.4)	0.65 (0.39–1.06)	19 (2.5)	0.51 (0.28–0.91)	31 (4.9)	1.0	34 (8.2)	1.88 (1.00–2.95)	45 (12.9)	3.06 (1.88–4.98)
Macrosomia	4 (0.4)	0.27 (0.07–1.05)	3 (0.4)	0.44 (0.11–1.76)	6 (0.9)	1.0	3 (0.7)	0.84 (0.21–3.41)	4 (1.1)	1.27 (0.35–4.59)
PIH	68 (7.4)	0.57 (0.38–0.88)	47 (6.3)	0.84 (0.55–1.30)	46 (7.2)	1.0	43 (10.4)	1.72 (1.00–2.69)	56 (16.0)	2.87 (1.86–4.42)
GDM	40 (4.3)	0.95 (0.58–1.57)	34 (4.6)	1.02 (0.61–1.70)	28 (4.4)	1.0	17 (4.1)	0.94 (0.51–1.75)	19 (5.4)	1.28 (0.70–2.32)
C/S	40 (4.3)	0.76 (0.45–1.26)	29 (3.9)	0.84 (0.49–1.44)	28 (4.4)	1.0	23 (5.6)	1.39 (0.78–2.46)	12 (3.4)	0.82 (0.41–1.65)
Postpartum hemorrhage	23 (2.5)	0.65 (0.35–1.19)	20 (2.7)	0.76 (0.41–1.41)	22 (3.5)	1.0	4 (1.0)	0.28 (0.09–0.81)	21 (6.0)	1.82 (0.91–3.22)
Laceration	171 (18.5)	0.88 (0.68–1.14)	144 (19.3)	0.96 (0.73–1.26)	123 (19.4)	1.0	72 (17.4)	0.9 (0.65–1.24)	79 (22.3)	1.26 (0.91–1.74)

CI: confidence interval; LBW: low birth weight, SGA: small for gestational age, LGA: large for gestational age; PIH: pregnancy induced hypertension, GDM: gestational diabetes, C/S: cesarean section; adjusted for maternal age, parity and prepregnancy BMI.

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assessment of the current JSOG guidelines for optimal weight gain.

Underweight women had a higher incidence of LBW infants than the normal group. Consistent with previous reports, in our study, low maternal prepregnancy BMI had a significant impact on perinatal outcomes, such as LBW and SGA [15–17]. In our study, 7.5% of the LBW infants and 11% of the SGA infants were attributed to women who were underweight at conception. Low maternal BMI could result from chronically poor energy intake, which would reduce fat stores and compromise visceral and somatic protein status. Poor maternal nutritional status during pregnancy has also been associated with reduced placental weight and surface area, which could limit nutrient transfer from the maternal circulation to the fetus, even if dietary intake increased later in pregnancy [18]. These findings indicate that an adequate BMI range before conception may help to prevent adverse perinatal complications.

On the other hand, in our study, obese women had a higher incidence of LGA infants, PIH and cesarean section deliveries. Vahratian et al. reported that overweight women (BMI > 26.1–29.0) and obese women (BMI > 29.0) were 1.2 and 1.5 times more likely, respectively, to have cesarean deliveries than women of normal weight (19.8 < BMI < 26.0) [19]. Many researchers reported that maternal obesity is associated with increased complications of pregnancy, labor, and delivery, infant macrosomia and birth defect, such as LGA infant, PIH and cesarean section deliveries [20–22]. Therefore, appropriate maternal BMI at conception may help to reduce the risk for pregnancy complications and adverse pregnancy outcomes.

However, the relation between prepregnancy BMI and the incidence of complications varied according to the maternal weight gain during pregnancy. Several investigators have suggested that the LBW risk among women with poor weight gain is increased if they also reported a low prepregnant BMI [23–24]. Our study found that the risk of LBW infants decreases when a woman's weight gain exceeds 8 kg, and the risk of PIH and cesarean section delivery decreases when women gain less than 14 kg. These results seem to support the importance of adequate maternal weight gain to avoid the incidence of perinatal complications even though the prepregnant BMI can be considered a potential predictor of adverse outcomes.

Birth weight is an important correlate of neonatal and infant health and has been recently associated with adult onset disease, including cardiovascular diseases, non-insulin dependent diabetes mellitus [25–27]. In addition, reduced ponderal index, which indicates asymmetric growth restriction is associated with reduced cognitive development and lower intelligence quotient in children [28–30]. A recent study showed that women delivering small infants may have a higher risk of heart disease than women having larger infants [31], and that women with PIH have a higher risk of hypertension and heart disease later in life [32]. These results seem to support the importance of appropriate birthweight and optimal weight gain of women in pregnancy to reduce adverse prenatal outcomes.

In regard to reduced birth size, the risk of LBW and SGA infant was high among the women with weight gain of less than 8 kg. They were nearly twice as likely to deliver LBW and SGA infants as those with weight gains of 10.1–12 kg. On the other hand, a low risk was found in women with weight gain more than 8 kg. This means an appropriate maternal weight gain may be a strong predictor of reduction of the risk of LBW and SGA infants. Thus, our findings highlight the importance of poor maternal weight gain as a potentially correctable cause of adverse perinatal outcomes.

LGA were associated with excessive weight gain during pregnancy [33]. Although normal women with more than 14 kg weight gain during pregnancy showed a three times greater risk for LGA infants, than the women with weight gains 10–12 kg, there was no significant association between maternal weight gain and the incidence of LGA among underweight and obese groups. Regarding the neonatal birth size, these results indicate that the upper limit of weight gain of up to 14 kg for women regardless of the prepregnant BMI is optimal and may result in absence of complications.

A few studies reported that excessive weight gain would induce a higher risk of adverse perinatal outcomes, PIH, GDM and cesarean delivery [1–5]. Optimal weight gain for Japanese pregnant women was set by JSOG in order to prevent the risk of PIH, in 1997 [8]. According to Murakami et al. [34], weight gain during pregnancy seems to have no significant influence on perinatal outcomes, such as GDM and PIH. They found that the incidence of PIH was not significantly increased in Japanese women who gained more than 12.5 kg compared to those gained 8.5–12.5 kg. They had different classification of maternal weight gain as follows: less 8.5 kg, 8.5–12.5 kg and over 12.5 kg, and analyzed the data using 8.5–12.5 kg as the reference group. Their finding was of great interest to clinicians, in assessing the effects of restricting weight gain on perinatal outcome. Consistent with their findings, our study found that GDM was not associated with weight gain. On the other hand, the incidence of PIH was higher among women gaining up to 14 kg. The reason for this inconsistency may be redefining classification for maternal weight gain and setting the references.

There are some limitations in our study. First, we did not find any significant relation between perinatal complications and maternal weight gain, possibly due to limited classification for obesity and weight gain range. NIH defined overweight as a BMI 25.0–29.9 kg/m^2 and obesity is a BMI > 30 kg/m^2 [10]. In our study, 9% were overweight and only 1.8% had obesity by NIH criteria (data not shown). The rate of obesity (BMI > 30 kg/m^2) among reproductive-aged women is around 33% in US [35], in 2000. On the other hand, although the prevalence of obesity is increasing and becoming a major risk factor for common disease for most Japanese people, BMI has been decreasing only in reproductive-aged women, presumably due to excessive

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dieting. The rate of obesity (BMI > 25 kg/m^2) among Japanese women aged 20–29 and 30–39 years old significantly had decreased over the last two decades, 1980–2000 (11.1 to 6.9%, 14.7 to 12.9%, respectively) [36].

Secondly, our sample size was small and too few women in this study had a diagnosis of GDM, PIH, macrosomia and postpartum hemorrhage during pregnancy. The rate of perinatal complications was examined in five stratified categories for weight gain based on prepregnancy BMI, making statistical differences. Thus, we believe large-scale randomized trials are needed to assess more precisely the acceptable range of weight gain for incidence of perinatal complications.

This study shows that the perinatal outcomes for women with a gestational weight gain of 8–10 kg and 12.1–14.0 kg were not significantly different from those for women with gestational weight gain 10.0–12.0 kg. Restricted weight gain is not strongly protective against maternal complications. This indicates that optimal weight gain should not be too low and current JSOG guidelines should be re-assessed. Our findings will be useful to clinicians providing antenatal care. Appropriate gestational weight gain is important for achieving healthy pregnancies, deliveries and birth outcomes for women. In addition, women who were underweight and obese before pregnancy should be aware of the potential hazards of low or high preconception BMI. We need to further research and validate clinically effective and practical interventions in optimizing better health outcomes for infants and mothers.

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Title: Risk factors for small for gestational age

Running title: Risk factors for SGA infants

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Abstract

Background: The purpose of the paper was to determine the risk factors for small for gestational age (SGA) infants at full term, in Japan.

Methods: The study was conducted at four hospitals and clinics in the Tokyo metropolitan area. A retrospective review of 2972 mothers and their infants born from singleton pregnancies at any time during the years 2002 and 2003 was conducted.

Results: Of these women, 8.4% gave birth to SGA infants. The proportion of SGA infant was significantly higher among heavy smokers (>10 cigarettes/day; 13.7%, $p<0.01$). The odds ratio for SGA decreased significantly in proportion to the pregnancy body mass index (OR 0.89, 95%CI. 0.84-0.94, $p<0.001$). The odds ratio of SGA for stratified maternal weight gain was 1.79 (95%CI. 1.24-2.58, p=<0.01) for weight gain less than 8.0 kg, 1.16 (95%CI. 0.79-1.71, $p=0.45$) for weight gain 8.0-10.0 kg, and 0.49 (95%CI.0.3-0.78, $p<0.01$) for weight gain over 12 kg.

Conclusion: Our study clearly confirms the detrimental effect of a low prepregnancy body mass index, low maternal weight gain and maternal smoking during pregnancy on the incidence of SGA infants.

Key Words small for gestational age (SGA), maternal weight gain, prepregnancy body mass index (BMI)

Introduction

Birth weight in infants is an important predictor not only of perinatal health, but also of growth, development and well-being in adult life.[1] Reduced size at birth, which includes low birth weight (LBW: birth weight less than 2500 g) and small for gestational age (SGA: the lowest 10th percentile for gestational age) infants are at greater risk than infants of normal birth weight, of having reduced educational capacity, school performance and intellectual development.[2]

Some adult health risks show a clear negative correlation with infant birth weight. The fetal origins hypothesis that low birth weight may be associated with an increased risk of subsequent development of a variety of complications in adulthood including cardiovascular disease, non-insulin dependent diabetes mellitus, hypertension and dyslipidemia.[1,3-4] In addition, a recent study reported that SGA was associated with adult psychological disorders as well. Wiles et al. reported that children born full term but weighing less than 5.5 lb had increased psychological distress in later life, and that 1 SD decrease in birth weight for gestational age was associated with increased psychological distress in adulthood.[5]

The Maternal and Child Health Statistics of Japan survey revealed that the average birth weight has gradually declined since 1985. Mean birth weights were 3.2 for boys and 3.12 kg for girls in 1985, and these declined to 3.07 and 2.99 kg, respectively in 2004, although there was no difference of average gestational age between those years.[6] It is important to identify the SGA risk factors that may reduce the incidence of infant mortality and morbidity, and

finally reduce the risk of diseases in later adulthood. The purpose of this study was to determine the risk factors for SGA infants at full term in Japan.

Materials and Methods

Subjects

The study was conducted at the obstetrics and gynecology divisions of four hospitals and clinics located in different administrative wards of the Tokyo metropolitan area. However the number of delivery per year of each hospitals and clinics was different, the average maternal age, parity, incidence of cesarean section for subjects, was similar. Therefore, we combined the data to analyze the risk factors for SGA. It is a retrospective study; undertake using data from 2972 Japanese mothers and their infants born at 37 to 41 weeks of gestation from singleton pregnancies at any time during the years 2002 and 2003. Exclusion criteria were as follows: stillbirth, fetal malformations, gestational or pregestational diabetes and pregnancy induced hypertension.

Anthropometric Measurements and Data Collection

Gestational age was estimated from the last menstrual period (LMP) and confirmed by ultrasound examination mainly at 8-11 gestational weeks. SGA was defined as the lowest 10th percentile for gestational age at birth in the population standard for gestational age, sex and parity according to the reference developed by Nishida et al,[7] which had commonly been used

as birth size standards for Japanese neonates.

Maternal prepregnancy weight was self reported. BMI was calculated as prepregnancy body weight divided by the square of height (kg/m^2). Subjects were classified according to the prepregnancy BMI into underweight (BMI<18.0), normal (18.0<BMI ≦ 24.0), and obese (BMI>24.0) groups, according to the standards set by the Japan Society of Obstetrics and Gynecology (JSOG). The WHO expert group has proposed that the range of normal BMI for Asian populations should be narrowed, because the WHO guidelines for BMI criteria (underweight<18.5, normal 18.5-25.0, and obese>25.0) are based on data from Western countries, and many Asian countries have a lower prevalence of obesity, yet have high rates of obesity-related diseases.[8] We used the BMI criteria formulated by the JSOG because the normal range specified by the JSOG is narrower than that of the WHO.

Other demographic data including age, parity and medical history were obtained from prenatal records. After delivery, the newborn anthoropometric characteristics and recorded; birth weight, length, head and chest circumference were measured. Total maternal weight gain was defined as the difference between measured weight at the last prenatal visit closest to delivery and self-reported prepregnancy weight. In the present study, the 25th, 50th, 75th and 90th percentiles for maternal weight gain are 7.4, 9.5, 11.7 and 14.0 kg, respectively. To examine the influence of increased maternal weight gain on birth weight or incidence of SGA, we stratified weight gain into four categories based on these percentile values; less than 8.0, 8.0-10.0, 10.1-12.0 and over 12.0 kg. Smokers were defined as women who had smoked