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ORIGINAL CONTRIBUTION

Dietary folate intake during pregnancy and birth weight in Japan

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Abstract *Background* Inadequate folate status has been associated with many negative reproductive outcomes, such as neural tube defects (NTD), low birth weight and placental abruption. *Aim of the study* The objectives of this study were to evaluate the levels of dietary folate intake during pregnancy in Japanese women and the subsequent birth weight of their babies. *Methods* A longitudinal prospective study was conducted with 197 women with a singleton pregnancy in 2005. Dietary folate was investigated 3 times: in the first trimester at 12 weeks, in the second trimester at 20 weeks and in third trimester at 32 weeks using a diet history questionnaire (DHQ). Non fasting blood samples were collected from the women for measurement of homocysteine, hemoglobin, ferritin, unbound iron-binding capacity (UIBC) and total iron-binding capacity (TIBC). *Results* Energy intake increased as pregnancy advanced, but not significantly. The daily intake of folate increased from 248.5 ± 113.1 μg/d in the first trimester to 275.4 ± 100.2 μg/d in the third trimester ($P = 0.04$). This was well below the recommended level of 440 μg/d and only 10% of mothers were above the levels. In the third trimester, plasma homocysteine concentration was significantly higher in the low folate group of less than 250 μg/d ($P = 0.02$), but not the first and second trimesters. Dietary folate intake and plasma homocysteine concentrations were not likely to be predictors of birth weight in our subjects. *Conclusions* Our study shows that Japanese women's energy and folate intakes do not meet their energy needs during pregnancy and are at an extremely low recommended dietary allowance level throughout pregnancy.

Key words dietary folate intake – pregnancy – maternal nutrition – birth weight

Introduction

The embryo and fetus are totally dependent on the maternal nutrient status and the maternal-fetal transfer of nutrients. An adequate diet is required during pregnancy to make up for the energy deposited in maternal and fetal tissues, and a high folate intake is also required because of increased folate utilization and catabolism [11]. In early pregnancy inadequate folate status has been associated with many negative reproductive outcomes, such as an increased risk of neural tube defects (NTD) [1,27] and recurrent spontaneous abortion [14]. In general, the

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recommended timing of folic acid administration is from before conception until the end of the first trimester. Recently, it has been reported that folate deficiency is also closely associated with placental abruption, pre-eclampsia [2, 16], anemia and preterm delivery [9, 17, 18] not only in the first trimester, but also in the second and third trimesters and/or throughout pregnancy. Scholl et al. reported that low folate intake (<240 μg folate/d) at week 28 was associated with a more than 3-fold increase in risk of infant low birth weight [21]. Goldenberg et al. [3] also reported an effect of lower serum folate at week 30 on reduced infant birth weight in Alabama women with risk factors for intrauterine growth restriction (IUGR). Therefore, appropriate folate levels may be important throughout pregnancy until full term, not only during the periconceptional period and early pregnancy.

In Japan, fortification of enriched grain product with folate is not compulsory or endorsed officially; however, 440 μg dietary folate intake with balanced meals was recommended to all Japanese women of reproductive age by the Ministry of Health and Welfare in 2000 to prevent birth defects [6]. However, the incidence of NTD births in Japan reduced by only 7% from 1991–2000 to 2001–2002 [24], which was a small change compared to other developed countries, such as the USA [23] and Canada [15]. In addition, the average birth weight of Japanese infants has gradually reduced since 1985 and the prevalence of low birth weight (LBW: birth weight less than 2,500 g) has increased [12]. Therefore, we conducted a prospective observational study to evaluate whether the information about additional folate intake had an influence on the maternal nutritional status of Japanese women. The objectives in this study were to evaluate the levels of dietary folate intake during pregnancy in Japanese women and the subsequent birth weight of their babies.

Materials and methods

Subjects

The study design was a longitudinal prospective study involving healthy pregnant women and age-matched non-pregnant women. The women subjects were attending antenatal care services at the Nagai Clinic, which is located in Misato City, Saitama, Japan, and which has approximately 1,800 deliveries a year. The subjects were recruited to the study during their first antenatal visit. All were at 6–8 weeks gestation and visited the clinic to confirm the conception between June and September in 2005. Gestational age was estimated from the first day of the last menstrual period, and fetal growth was confirmed by ultrasound examination at approximately 8–11 gestational weeks. Participating women underwent routine physical examinations during pregnancy, including blood pressure measurements, urine test, hematology, and ultrasound examination. Women with a clinical diagnosis of gestational or pregestational diabetes, pregnancy-induced hypertension, multiple deliveries, stillbirth, or fetal malformation were excluded from the study. The control subjects were recruited from the staff members in the same clinic and matched for age and BMI. They were not taking any prescribed medication, including oral contraceptives.

Anthropometric measurements

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 [5]. Weight gain was measured at each physical check-up. Total pregnancy weight gain was defined as the difference between the self-reported pre-pregnancy weight and the measured weight at the last prenatal visit close to delivery. Other demographic data, including age, parity and medical history, were obtained from the prenatal records. Infants' birth weight and length were measured after delivery. Smokers were defined as women who had smoked any number of cigarettes during pregnancy, regardless of smoking status before conception: participants were classified as nonsmokers or smokers.

Dietary assessment

Dietary habits during the last month of gestation were assessed with a self-administered diet-history questionnaire (DHQ), which was completed by each mother while waiting for the medical examination. The DHQ took approximately 20 min to complete. Data were obtained 3 times: at 12, 20, and 32 weeks. The DHQ is a 16-page structured questionnaire, consisting of the following 7 sections: general dietary behaviors, major cooking methods, consumption frequency and portion size of 6 alcoholic beverages, semiquantitative frequency of intake of 121 selected food and nonalcoholic beverage items, dietary supplements, amount and consumption frequency of 19 staple foods (rice, bread, noodles, and other wheat foods), and open-ended items for foods consumed regularly (≥1 time/week) but not appearing in the DHQ. The food and beverage items and portion sizes in the DHQ were derived primarily from the National Nutrition Survey of Japan data and several recipe books for Japanese dishes [20]. Measures of dietary intake for 147 food and beverage items, energy, fat, total carbohydrates, alcohol and dietary fiber were calculated by using an ad hoc computer algorithm developed for the DHQ, which was based on the Standard Tables of Food Composition in Japan [22].

Blood collection and analysis

Pregnant women had non-fasting blood samples collected at 12, 20 and 32 weeks of gestation for measurement of homocysteine, hemoglobin, ferritin, UIBC and TIBC. Blood samples were drawn from the antecubital vein in potassium ethylenediaminetetraacetic acid (EDTA) and serum separator tubes, and then centrifuged for 10 min at 3,000*g* to separate the serum, which was stored at −80°C until analysis. Plasma was removed and stored at −80°C until analysis. Serum albumin was assayed using an enzymatic method. UIBC and TIBC were measured by competitive protein binding assay (Quick auto Neo UIBC Kit and Quick Neo Fe kit, Sino test co, Japan). Serum ferritin was measured by a chemiluminescent immunoassay (N-Assay TIA Kit, Nitobo, Japan). Plasma homocysteine was measured by an enzymatic colorimetric assay using a single wavelength of 660 nm (AZWELL Auto Hcy Kit, Alfresa co, Japan) [10].

Statistical analysis

Nutritional intakes were analyzed in each trimester and compared to the control. Dietary folate intake was divided into two groups according to the median: low folate group (dietary folate intake <250 μg/d) and high folate group (≥dietary folate intake 250 μg/d). Differences in continuous variables were determined by independent *t* test, the Mann–Whitney–Wilcoxon test for non-normally distributed data or repeated measures ANOVA. Multiple regression analyses were performed after adjustment for possible confounding factors, such as gestational weeks, infant sex and maternal smoking. A *P*-value <0.05 was considered to be statistically significant. Statistical analysis was carried out with SPSS for Windows, version 12.0 (SPSS Inc, Chicago, III, USA).

The study was approved by the Ethics Committees of the University of Tokyo and Nagai Clinic. Written consent was obtained from all participants, after obstetricians explained the purpose, significance, and protocol of the study.

Results

Of 220 pregnant women initially recruited, 197 successfully completed the study. Table 1 shows the demographic characteristics of mothers and infants, and of 30 non-pregnant women in the control group. In pregnant women, the average maternal age (±SD) was 30.8 ± 4.5 years old. Their average BMI (±SD) was 21.0 ± 3.6 kg/m^2. Out of 197, 44(22.3%) were classified according to pre-pregnancy BMI as underweight, 131 (66.5%) as normal, and 22 (11.2%) as obese. No significant difference in weight gain was observed between the pre-pregnancy BMI categories. On the other hand, in the non-pregnant women, the average age and BMI (±SD) were 29.4 ± 4.3 years old and 21.0 ± 3.0 kg/m^2, respectively. There was no significant difference in age or BMI between the pregnant and non-pregnant women. The percentages of smokers in the preconception and pregnant groups were 20.3 and 10.7%, respectively. The mean gestational duration (±SD) was 38.9 ± 1.0 weeks. The mean birth weight (±SD) was higher for male infants than for female infants (3074.4 ± 337.5 g vs 2949.8 ± 328.2 g, $P < 0.03$).

Table 2 shows the mean daily nutrient intake throughout pregnancy. The mean total energy intake for pregnant women was 1723.0 ± 591.6, 1754.8 ± 442.3, and 1792.5 ± 442.9 kcal, in the first, second and third trimesters, respectively. The energy intake increased as pregnancy advanced, but not significantly. The mean total energy intake for non-pregnant women was 1722.9 ± 444.4 kcal. No significant difference was observed throughout the trimesters between pregnant women and non-pregnant women. In pregnant women, the intake of folate increased from 248.5 ± 113.1 g in the first trimester to 275.4 ± 100.2 g in the third trimester ($P = 0.04$). However, the daily intake amounts were well below the recommended levels. There was no significant difference between pregnant and non-pregnant women in this respect.

Table 3 shows the medians and percentiles of energy intakes from Vitamin B6, B12 and folate throughout pregnancy. In pregnant women, only the intake of vitamin B12 was above RDA levels. Regarding folate intake, almost all mothers were below the RDA levels throughout pregnancy.

Maternal biomakers for the low and high folate intake groups are shown in Table 4. In the first and second trimesters, there was no significant difference in biomarkers between the low and high groups. In the third trimester, plasma homocysteine concentration was significantly higher in the low folate group ($P = 0.02$).

Table 5 shows the association of dietary intakes and plasma homocysteine concentrations with birth weight, using multiple regression analyses controlling for maternal age, parity and infant sex. The analysis indicated that dietary folate intake was the only predictor of birth weight, but not significantly in the third trimester ($P = 0.06$). The other factors including

Table 1 Maternal and infants' demographic characteristics

	Pregnant women (n = 197)		*P*-values	Control (n = 30)[a]		*P*-values*
	Mean ± SD	Range		Mean ± SD	Range	
Mother						
Age (years)	30.8 ± 4.5	19–42		29.4 ± 4.3	19–34	0.08
Height (cm)	157.9 ± 5.4	145.0–173.5		158.1 ± 6.2	147.0–171.0	0.32
Prepregnancy BMI (kg/m^2)	21.0 ± 3.6	16.7–36.9		21.0[b] ± 3.0	17.9–30.5	0.80
Underweight *n*(%)	44 (22.3)		NS			
Normal *n*(%)	131 (66.5)					
Obese *n*(%)	22 (11.2)					
Maternal weight gain (kg)						
Underweight	10.1 ± 3.1	0.8, 7–16.6	NS			
Normal	9.3 ± 3.5	0.1–21.0				
Obese	8.5 ± 3.9	−7.3 to 21.5				
Primipara (%)	50.3			60.0		
Smoking						
Preconception (%)	17.4					
During pregnancy (%)	7.4					
Anemia						
First trimester (%)	17.8					
Second trimester (%)	34.0					
Third trimester (%)	36.5					
Infant						
Gestational weeks (w)	38.9 ± 1.0	37–41				
Birth weight (g)						
Boys	3,077 ± 321.2	2,245–3,750	0.03			
Girls	2.994 ± 348.7	225–3,610				
Birth length (cm)	48.7 ± 1.6	43.9–51.9				
Ponderal index (kg/m^3)	26.2 ± 1.9	20.6–31.1				
Placenta weight (g)	563.4 ± 93.6	350–850				

Values are presented as mean ± SD or *n*(%). Underweight (BMI < 18.5 kg/m^2), Normal (18.5 ≤ BMI < 25.0 kg/m^2), Obese (BMI ≥ 25.0 kg/m^2)
NS non significant
**P* values: Pregnant women vs. Control (*t* test)
[a]Control:Non-pregnant women
[b]Current BMI

Table 2 Mean daily intakes of nutrition throughout pregnancy

	Pregnant women (n = 197)			RDA	*P* values** (1st vs. 2nd and 3rd trimesters)	Control (n = 30) (Non-pregnant women:n = 30)		*P* values* (control vs pregnant women)
	First trimester	Second trimester	Third trimester					
	Mean ± SD	Mean ± SD	Mean ± SD			Mean ± SD	RDA	
Total energy (kcal)	1723.0 ± 591.6	1754.8 ± 442.3	1792.5 ± 442.9	‡	0.40	1722.9 ± 444.4	†	0.74
Protein (g)	53.4 ± 21.1	57.1 ± 21.5	59.7 ± 17.2	70	0.005	54.8 ± 19.3	60	0.60
% energy from total fat (%)	27.2 ± 6.0	28.7 ± 5.1	29.3 ± 5.6	20–30	0.01	27.5 ± 6.3	20–30	0.46
% energy form carbohydrate (%)	59.6 ± 7.1	57.4 ± 5.9	56.6 ± 6.3	50–70	<0.001	53.5 ± 7.4	50–70	0.002
Calcium (mg)	470.9 ± 228.7	521.5 ± 213.4	553.5 ± 234.5	700	0.002	417.3 ± 219.0	600	0.038
Iron (mg)	5.7 ± 2.4	6.1 ± 1.9	6.3 ± 2.0	10.5	0.02	5.6 ± 2.1	10.5	0.29
Vitamin A (μg)	542.9 ± 569.2	588.6 ± 452.7	632.7 ± 498.7	600	0.24	540.0 ± 425.0	600	0.22
Vitamin B1 (mg)	0.7 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	1.1	0.06	0.7 ± 0.3	1.1	0.24
Vitamin B2 (mg)	1.17 ± 0.5	1.3 ± 0.4	1.3 ± 0.4	1.2	0.06	1.1 ± 0.4	1.2	0.13
Vitamin B6 (mg)	0.8 ± 0.4	0.9 ± 0.3	0.9 ± 0.3	2	0.008	0.9 ± 0.4		0.64
Vitamin B12 (mg)	4.8 ± 3.6	5.2 ± 2.8	5.5 ± 2.9	2.8	0.09	5.5 ± 2.9		0.58
Folate (μg)	248.5 ± 113.1	261.6 ± 94.3	275.4 ± 100.2	440	0.043	254.3 ± 120.3	200	0.72
Vitamim C (mg)	103.8 ± 69.2	96.4 ± 50.7	104.8 ± 57.2	100	0.33	86.9 ± 76.2	100	0.24
Vitamin D (μg)	4.8 ± 3.4	5.0 ± 2.8	5.3 ± 3.2	5	0.41	5.9 ± 3.6	5	0.19

Values are presented as mean ± SD. RDA: Mean values of recommended dietary allowances for physical activity level II in 2005. RDA for total energy is 2,000 kcal for non-pregnant women. RDA for total energy is 2,050 in the first, 2,250 in the second and 2,500 Kcal in the third trimester for pregnant women
**P* values: control vs. pregnant women (Mann–Whitney *U* test)
***P* values: 12 weeks vs. 20 and 32 weeks (repeated-measures ANOVA)

Table 3 Daily nutrient intake throughout pregnancy

	Percentile						
	5	10	25	50	75	90	95
Energy intakes (Kcal)							
First trimester	861.9	1005.8	1320.0	1643.6	2056.0	2430.4	2812.9
Second trimester	1104.2	1220.7	1512.0	1721.9	2002.1	2339.4	2605.9
Third trimester	1111.9	1241.6	1472.9	1821.3	2081.5	2342.5	2483.3
Control	1109.7	1166.5	1387.7	1679.8	1964.1	2489.3	2713.2
Dietary vitamin B6 (mg)							
First trimester	0.3	0.4	0.6	0.8	1.0	1.3	1.4
Second trimester	0.4	0.6	0.7	0.8	1.1	1.3	1.6
Third trimester	0.5	0.6	0.7	0.9	1.1	1.4	1.5
Control	0.4	0.4	0.6	0.9	1.1	1.6	1.8
Dietary vitamin B12 (mg)							
First trimester	1.3	1.7	2.7	4.1	6.1	7.9	8.8
Second trimester	1.8	2.3	3.1	4.8	6.6	9.4	11.0
Third trimester	2.0	2.4	3.4	5.1	6.9	9.5	12.1
Control	1.7	2.2	3.1	5.0	6.9	10.8	10.9
Dietary folate (μg)							
First trimester	98.9	134.3	171.2	231.7	296.1	364.1	402.2
Second trimester	133.3	156.0	196.1	243.6	309.8	380.5	415.2
Third trimester	140.3	161.4	203.9	264.4	334.0	416.8	474.7
Control	91.0	136.4	171.6	235.9	271.9	426.5	573.1

Table 4 Mean of maternal biomarkers by dietary folate intake

First trimester	<250 μg *n* = 101 (55.8%)	≥250 μg *n* = 80 (44.2)	*P*
Plasma homocysteine (μM)	5.7 ± 2.5	5.3 ± 2.2	0.08
Hemoglobin (g/dl)	12.6 ± 9.8	11.8 ± 0.7	0.21
Serum ferritin (μg/dl)	119.9 ± 40.7	122.0 ± 39.0	0.97
UIBC (μg/dl)	232.9 ± 75.4	248.6 ± 79.2	0.11
TIBC (μg/dl)	348.9 ± 63.5	370.6 ± 64.9	0.06
Second trimester	*n* = 97 (51.6%)	*n* = 91 (48.4%)	*P*
Plasma homocysteine (μM)	5.2 ± 1.9	5.2 ± 1.9	0.63
Hemoglobin (g/dl)	11.3 ± 0.7	11.2 ± 0.8	0.09
Serum ferritin (μg/dl)	116.5 ± 42.8	106.4 ± 42.6	0.08
UIBC (μg/dl)	311.4 ± 103.6	321.0 ± 1111.1	0.62
TIBC (μg/dl)	427.9 ± 81.9	423.6 ± 96.5	0.77
Third trimester	*n* = 87 (46.5%)	*n* = 100 (53.5%)	*P*
Plasma homocysteine (μM)	6.0 ± 2.4	5.4 ± 2.4	0.02
Hemoglobin (g/dl)	11.2 ± 0.6	12.2 ± 9.7	0.89
Serum ferritin (μg/dl)	77.2 ± 67.6	92.6 ± 85.0	0.17
UIBC (μg/dl)	464.4 ± 129	450.9 ± 118.6	0.54
TIBC (μg/dl)	534.5 ± 106.2	524.9 ± 120.9	0.69

dietary B6, B12 intakes and plasma homocysteine in all trimesters were not related to infant birth weight.

Discussion

Consistent with the findings of the Japan National Nutrition Survey [19], we found that the majority of mothers did not follow the RDA guidelines during pregnancy. A possible reason may be that well-nourished women require only a small amount of additional energy because the body adapts to its energy requirements; it becomes more energy efficient through reduced physical activity and a lowered metabolic rate. Weight gain management may potentially be another variable that influences nutrition during pregnancy. Ueda et al. found that maternal weight gain during pregnancy and birth weight had decreased by approximately 2 kg from 1988 to 2002, with the aim of delivering smaller infants with less delivery complications [26].

In our subjects, although folate intake had gradually increased throughout the trimesters, only 10% of the women met the pregnancy recommendations for folate intake. Mito et al. [13] reported that more than 80% of Japanese women aged between 17 and 41 had inadequate folate intake in 2002. In the study conducted by Kondo et al. [6] in 2002–2004, the reported rate of awareness of the importance of dietary folate intake was l3% for young Japanese women and 15% for mothers who had already given birth. Our findings do not suggest that the folate intake RDA is too high for Japanese women because a deficiency in folic acid can lead to neural tube defects in the offspring [1, 27]. However, awareness of the importance of adequate folate intake has not improved in Japanese women since 1998, the year the guidelines on folate intake were issued. Therefore, we should place greater emphasis on this issue and discuss how the RDA guideline can work more effectively with the public.

We found that plasma homocysteine concentrations were higher in women with low dietary folate

Table 5 Multiple regression analyses to evaluater the association of various parameters in each trimester with birth weight

	First trimester		Second trimester		Third trimester	
	Effect size	*P*	Effect size	*P*	Effect size	*P*
Dietary						
Vitamin B6	124.7	0.38	48.5	0.71	208.7	0.13
Vitamin B12	3.8	0.78	−5.3	0.66	−10.6	0.34
Folate	−0.6	0.21	−0.2	0.63	−0.8	0.06
Plasma homocysteine	−10.8	0.28	−11.2	0.36	−10.8	0.86
Maternal smoking (vs non-smoking)	−136.1	0.09	−146.8	0.06	−136.1	0.11
Prepregnancy BMI	15.9	0.02	14.5	0.03	15.9	0.07
Gestational age (weeks)	105.6	<0.001	104.1	<0.001	105.6	<0.001

Adjusted for maternal age, parity and infant sex

intake <250 μg/d than in women subjects with an intake of ≥250 μg/d, in the third trimester, but not in the first and second trimesters. Plasma total homocysteine concentration is regulated by folate as a high folate reduces the homocysteine levels. Folate is essential for DNA and RNA biosynthesis and is required for homocysteine metabolism. Yajnik et al. [28] reported that higher maternal plasma homocysteine concentration was significantly associated with lower birth weight ($r = -0.28$). In our study, using a multiregression analysis, we found that dietary folate intake and plasma homocysteine concentrations were not likely to be predictors of birth weight. However, conflicting results for other Japanese subjects have been recently published [25]. The possible reasons may by controlled for different confounding factors in multiple regression analysis. The extent to which maternal folate nutrition affects fetal growth could not be determined, because of the lack of sufficient statistical evidence due to small sample sizes. Thus, the influence of maternal folate status on birth size remains controversial.

A strength of the current study was that we examined maternal nutritional status longitudinally. Almost all previous published studies in Japan were cross-sectional [13, 25]. However, there are a number of limitations inherent to this study. First, we did not have data on serum folate concentrations as a biomarker of nutritional status. In most studies, serum or plasma folate concentrations are used as indicators of folate status. However, folate intake and circulating serum concentrations are positively correlated in pregnant and non-pregnant subjects [4, 8] Therefore, the folate status can be assumed from a measurement of dietary intake folate. Second, we did not investigate the percentage of these subjects that consumed folic acid supplements or folic acid enriched food. Kondo et al. reported that only 12% of pregnant Japanese women took folic acid tablets [7]. In addition, fortification of enriched grain product with folate is not endorsed in Japan. Therefore, it is not likely that folic acid supplement intake may have a major impact on the findings in the present study. Third, our sample size was small. Even though a significant difference emerged from a comparison of these groups, the results should be interpreted carefully.

In summary, our study showed that Japanese women's mean dietary folate intake was barely half of the recommended value and was at an extremely low level throughout pregnancy. The key contributing factor to this seems to be that the RDA guidelines have not led to a change in the public's folate intake. Pregnancy can be an opportune time to improve nutrition and presents an ideal time for health promotion activities. Health care providers should encourage all women of reproductive age to have a well-balanced diet behavior which leads to improved birth outcomes.

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References

1. Botto LD, Moore CA, Khoury MJ, et al (1999) Neural-tube defects. N Engl J Med 341:1509–1519
2. George L, Mills JL, Johansson ALV, et al (2002) Plasma folate levels and risk of spontaneous abortion. JAMA 288:1867–1873
3. Goldenberg RL, Tamura R, Cliver SP, et al (1992) Serum folate and fetal growth retardation: a matter of compliance? Obstet Gynecol 79:719–722
4. Jaccques PF, Sulsky SI, Sadowski JA, et al (1993) Comparison of micronutrient intake measured by a dietary questionnaire and biochemical indicators of micronutrient status. Am J Clin Nutr 57:182–189

5. Japan Society for the Study of Obesity (2000) Novel criteria for "obesity disease" in Japan on the recommendation of Japan Society for the Study of Obesity. J Jpn Soc Stud Obes 6:18–28
6. Kondo A, Kamihira O, Gotoh M, et al (2007) Folic acid prevents neural tube defects: international comparison of awareness among obstetricians/gynecologists and urologists. J Obstet Gynecol R 33:63–67
7. Kondo A, Kamihira O, Shimosuka Y, et al (2005) Awareness of the role of folic acid, dietary folate intake and plasma folate concentration in Japan. J Obstet Gynecol Res 31:172–177
8. Kondo A, Kimura K, Isobe Y, et al (2003) Folic acid reduces risks of having fetus affected with neural tube defects: dietary food folate and plasma folate concentration. Nippon Hinyokika Gakkai Zasshi 94:551–559. (in Japanese)
9. Lindblad B, Zaman S, Malik A, et al (2005) Folate, vitamin B12 and homocysteine levels in South Asian women with growthretarded fetuses. Acta Obstet Gynecol Scand 84:1055–1061
10. Matsuyama N, Yamaguchi M, Toyosato M, Takayama M, Mizuno K (2001), New enzymatic colorimetric assay for total homocysteine. Clin Chem 47:2155–2157
11. McPartlin J, Halligan A, Scott JM, Darling M, Weir DG (1993) Accelerated folate breakdown in pregnancy. Lancet 431:148–149
12. Ministry of Health, labour, Welfare, Japan, Mothers' and Children's Health Division (2004) Maternal and child health statistics of Japan. Mothers' and Children's Health Organization, Tokyo
13. Mito N, Takimoto H, Umegaki K, et al (2007) Folate intakes and folate biomarker profiles of pregnant Japanese women in the first trimester. Eur J Clin Nutr 61:83–90
14. Nelen WL, Blom HJ, Steegers EA, et al (2000) Homocysteine and folate levels as risk factors for recurrent early pregnancy loss. Obstet Gynecol 95:519–524
15. Persad VL, Van den Hof MC, Dube JM, Zimmer P (2002) Incidence of open neural tube defecs in Nova Scotia after folic acid fortification. CMAJ 167:241–245
16. Refsum H (2001) Folate, vitamin B12 and homocysteine in relation to birth defects and pregnancy outcome. Br J Nutr 85(Suppl):S109–S113
17. Relton CL, Pearce MS, Burn J, Parker L (2005) An investigation of folate-related genetic factors in the determination of birthweight. Paediatr Perinat Epidemiol 19:360–367
18. Relton CL, Pearce MS, Parker L (2005) The influence of erythrocyte folate and serum vitamin B12 status on birthweight. Br J Nutr 93:593–599
19. Research Group for Health, Nutrition Information (2004) The national nutrition survey in Japan, ministry of health, labour and welfare, Japan: results of 2002 survey. Daiichi Shuppan Publishing, Tokyo. (in Japanese)
20. Sasaki S, Yanagibori R, Amano K (1998) Self-administered diet history questionnaire developed for health education: a relative validation of the test-version by comparison with 3-day diet record in women. J Epidemiol 8:203–215
21. Scholl TO, Hediger ML, Schall JI, Khoo CS, Fisher RL (1996) Dietary and serum folate: their influence on the outcome pregnancy. Am J Clin Nutr 63:520–525
22. Science, Technology Agency, Japan (2000) Standard tables of food composition in Japan, 5th edn. Printing Bureau of the Ministry of Finance, Tokyo, (in Japanese)
23. Stevenson RE, Allen WP, Pai GS, et al (2000) Decline in prevalence of open neural tube defects in a high-risk region of the United State. Pediatrics 106:677–683
24. Sumiyoshi Y (2004) A study on monitoring of congenital anomalies. The Ministry or Health, Labour, Welfare, Tokyo, (in Japanese)
25. Takimoto H, Mito N, Umegaki K, et al (2007) Relationship between dietary folate intakes, maternal plasma total homocysteine and B-vitamins during pregnancy and fetal growth in Japan. Eur J Nutr 46:300–306
26. Ueda Y, Maruo M, Ashitaka Y, Honda Y, Miyama T (2004) Studies on the validity of the present criteria for optimal maternal weight gain during pregnancy: reevaluation of the changes in maternal and neonatal weight occurring during the period of 15 years beginning from 1988. Adv Obstet Gynecol 57:121–130, (in Japanese)
27. US Food, Drug Administration (1996) Food standards: amendment of standards of identity for enriched grain products to require addition of folic acid. Fed Regist 61:878–897
28. Yajnik CS, Deshpande SS, Panchanadikar AV, et al (2005) Maternal total homocysteine concentration and neonatal size in India. Asia Pac J Clin Nutr 14:179–181