Original Article

Low body weight gain, low white blood cell count and high serum ferritin as markers of poor nutrition and increased risk for preterm delivery

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This study determined factors of preterm delivery in Taiwan. Healthy women (n=520, age 29.1±4.2 y) at 8–12 weeks of pregnancy were recruited from prenatal clinics. Background information, anthropometrics, biochemical parameters, and dietary intake, collected by 24 h-recall were obtained from the first, second, and third trimesters to delivery. Clinical outcomes of neonates were also collected. The results show that 53.7% of women were primiparous and that the incidence of preterm delivery was 6.2%. Body weight gains in the first trimester and throughout pregnancy were significantly lower in mothers with preterm delivery (preterm group) than in mothers with term delivery (term group, $p<0.05$). Maternal cholesterol intake, circulating white blood cell counts (WBC) and serum albumin were significantly lower and that serum magnesium and ferritin were significantly higher in the preterm group than in the term group. Maternal weight gain was positively correlated with caloric and nutrient intake ($p<0.05$). Neonatal birth weight was positively correlated with maternal weight gain and intakes of protein and phosphate during pregnancy; with intakes of calories, vitamin B-1 and B-2 in the first trimester; and with intakes of calcium, magnesium, iron and zinc, as well as circulating WBC in the third trimester. However, neonatal birth weight was negatively correlated with serum iron in the third trimester and with serum iron and ferritin at the time of delivery. In conclusion, maternal weight gain in early pregnancy and WBC, mineral intake and iron status in late pregnancy seem to be major factors affecting delivery and neonatal outcomes.

Key Words: nutrient intake, maternal weight gain, white blood cells, ferritin, preterm delivery

INTRODUCTION

Preterm birth, the leading cause of perinatal morbidity and mortality in developed countries, is defined as a baby born at less than 37 weeks gestational age. It accounts for approximately 75% of neonatal morbidity and 70% of neonatal deaths and results in the increased risk of neurocognitive deficits, pulmonary dysfunction and ophthalmologic disorders in surviving preterm babies.[1] In the past several decades, there has been considerable progress in the survival rate and treatment in prematurity-associated complications and defects; however, the prevalence of preterm birth increased from 9.5% in 1981 to 12.7% in 2005 in the USA, an increase of 33%.[2] This increase indicates that an understanding of the applicable causes and mechanisms may lead to possible solutions to decrease the incidence of preterm births.

It has been shown that low body mass index (BMI) before pregnancy and inadequate body weight gain of pregnant women in the second and third trimesters are significantly associated with spontaneous preterm delivery in the USA and Europe.[3-5] In China, maternal BMI was associated with reduced fetal growth but not with preterm delivery.[6] Evidence supports the concepts that embryonic and fetal nutritional deficiencies, especially micronutrient deficiencies are significant contributors to the occurrence of birth defects. In addition, the frequency and severity of pregnancy complications may be reduced through an improvement in the micronutrient status of the mothers.[7] In pregnant adolescent and adult women, low intakes of calcium, magnesium, zinc, iron, fiber, folate, vitamin D, and vitamin E have been observed.[8] Several studies suggested that multivitamin and mineral use before and during pregnancy may potentially prevent preterm birth.[9-10] However, there is no enough evidence to show that multinutrient supplementation may reduce preterm delivery.[11-13]

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Manuscript received 16 November 2011. Initial review completed 3 July 2012. Revision accepted 27 August 2012.
doi: 10.6133/apjcn.2013.22.1.05

To investigate the relationships between a person's mineral status, such as that of: iron, calcium, magnesium, and zinc, and preterm birth, several maternal mineral-associated biomarkers have been evaluated. For example, early pregnancy hemoglobin concentrations were related to preterm birth in a U-shaped manner, and serum ferritin concentrations greater than 40 μg/dL at 34 weeks of gestation were sensitive in predicting preterm delivery.[14-16] In addition, serum magnesium concentrations less than 1.4 mg/dL may be a marker for preterm delivery.[17] Furthermore, serum deficiencies in total calcium, phosphorus and magnesium may induce premature uterine contractility and may result in preterm delivery.[18] Preterm infants small for their gestational age had low counts of different leukocytes, suggesting that preterm infants have less developed immune systems.[19] So far, there is no solid evidence to indicate that an improvement of maternal mineral status and leukocyte counts may reduce preterm delivery and adverse birth outcomes. In the present study, we assessed the relationship between nutrient intake and serum biochemical parameters during pregnancy in women with term and preterm delivery to search for biomarkers of preterm birth. We aimed to find predictors of preterm delivery to decrease the prevalence of preterm birth.

SUBJECTS AND METHODS

Subjects

From years 2005 to 2007, 520 healthy pregnant women were recruited from prenatal clinics of one hospital and one medical center in Changhua, Taiwan. Criteria for inclusion were singleton pregnancy and a gestational age (GA) of less than 16 weeks. GA was confirmed by ultrasound. Exclusion criteria included the inability to provide informed consent and chronic diseases, such as cardiovascular disease, diabetes, renal disease, and hypertension. Written consent was obtained from all participants; for those who were under 18 years old, the written consent was co-signed by a parent or legal guardian. Ethical approval was obtained from the Institutional Review Board of the Changhua Christian Hospital Ethics Committee (IRB No: CCH-93-09-08). When women delivered babies with a GA less than 37 weeks, the neonates and mothers were assigned to the preterm group. When women delivered babies with a GA equal to or greater than 37 weeks, the neonates and mothers were assigned to the term group.

Data collection

After enrollment, women were interviewed on three occasions based on their scheduled prenatal care visits; before 16 complete weeks of pregnancy (first trimester), between 17 and 24 weeks of pregnancy (second trimester), and between 28 and 34 weeks of pregnancy (third trimester). During the first interview, information concerning the subject's background, pregnancy, medical history, and social circumstances was obtained. Height was measured at the first interview, and weight was measured at all interviews by registered nurses using a stadiometer. Data about the course of pregnancy, including complications and pregnancy outcome were attained from hospital records.

During each face-to-face interview, a dietary assessment was conducted by trained interviewers using a 24-hr recall questionnaire accompanied with tools for serving size estimation. The tools included a dozen bowls of various sizes, a transparent plastic board with grid lines, and measuring cups and spoons. Information was obtained on cooking methods, location, time, sauces, and supplements. The results of serving sizes were transformed to food weights by the equations established by the Department of Nutritional Science at Fu Jen Catholic University.[20] Using food weights, daily nutrient intake was then calculated according to the Nutrient Composition Data Bank for Foods of Taiwan Area.[21]

Laboratory methods

A five milliliter venous blood sample was collected in each interview and at delivery from the women. Whole blood was refrigerated and sent for analysis on the same day. Complete blood counts, including white blood cells (WBC), red blood cells (RBC), hemoglobin, hematocrit, and platelets, were measured using an automatic hematology analyzer (GEN'S, Coulter Inc, FL). Serum albumin concentrations were measured by the Bromcresol Purple BCP method (Beckman Coulter DXC-800). Serum total calcium and magnesium concentrations were measured by the ion selective electrodes method (Beckman Coulter DXC-800). Serum iron and ferritin concentrations were measured by the Ferro Zinc method (Beckman Coulter, DXC-800) and the two-site immunoenzymatic assay (Beckman Coulter, UniCel DXI-800), respectively.

Statistical analysis

Statistical analyses were conducted with SAS 9.2 software (SAS Institute Inc, Cary, NC). Values are expressed as the means±SD. Student's t test for continuous variables and chi-square statistics for categorical variables were used to investigate the differences in the characteristics of mothers and neonates between the preterm and term groups. To evaluate the group effect, the time effect, and the interactions between group and time on maternal nutrient intake and blood biochemical parameters, we analyzed data from the three trimesters and delivery using a mixed effects model. In addition, the Bonferroni-Dunn post-hoc test was used to compare the differences among the three trimesters and the delivery and the differences between the mothers of preterm and term neonates. Moreover, Pearson simple linear correlation was used to investigate the relationships between maternal nutrient intake and biochemical parameters with maternal body weight gain and neonatal birth weight and lengths. Statistical significance was assumed at $p<0.05$.

RESULTS

A total of 520 pregnant women (mean age 29.1±4.2 yr) were recruited, and 53.7% were primiparous. Of the total, 451 women (86.7%) completed the study and gave birth between October 2005 and May 2007. The most common reason for withdrawing from this study (n=49) was a transfer to another hospital. The incidence of premature birth was 6.2% (n=28). Women who completed participation had a mean age of 29.3±4.0 years (range from 15 to 41 yr); 68.3% of them had completed college, 21.2% of them were homemakers, 1.5% of them were smokers, and 3.5% of them drank alcohol. Before pregnancy, the

Table 1. Characteristics of mothers and neonates in the preterm and term groups

	Term		Preterm		p-value[†]
	no	Mean±SD	no	Mean ± SD	
Mothers					
Age, y	423	29.2±4.0	28	30.4±4.3	0.120
Height, cm	423	160±5.0	28	159±6.0	0.261
Pre-conceptional BW[‡], kg	423	54.2±8.1	28	54.9±9.4	0.633
Pre-conceptional BMI[‡]	423	21.2±3.1	28	21.8±3.7	0.308
Total BW gain, kg	423	14.4±4.5	28	11.4±6.2	0.015
Average BW gain for each trimester, kg/wk					
1st trimester	422	0.19±0.16	28	0.13±0.18	0.050
2nd trimester	422	0.54±0.17	28	0.49±0.24	0.177
3rd trimester	422	0.44±0.19	24	0.43±0.33	0.870
Neonates					
Gestational age, week	423	39.2±1.0	28	34.5±3.6	<0.001
Birth weight, g	423	3165±351	28	2271±659	<0.001
Body length, cm	423	50.6±1.9	28	45.1±5.6	<0.001
Ponderal Index, kg/m^3	423	2.45±0.22	28	2.39±0.28	0.254
Placental weight, g	365	543±106	23	442±92	<0.001
Male/Female, %	226/197	53.4/46.6	11/17	39.3/60.7	0.146

[†]p-values were obtained from Student's t-tests for continuous variables and chi-square tests for proportions.
[‡]BW, body weight; BMI, body mass index.

average BMI of the women was 21.2±3.2. Most of the women (70.3%) were within the normal BMI range of 18.5 to 24, although 15.1, 8.2 and 6.4% of the women were underweight (BMI <18.5), overweight (24< BMI ≤27), and obese (BMI >27), respectively, based on the standards established by the Department of Health, Executive Yuan, Taiwan, R.O.C.

The characteristics of mothers and neonates are shown in Table 1. There were no significant differences in maternal age, body height, preconceptional body weight, or preconceptional BMI between the preterm and term groups. Mothers in the preterm group had significantly lower total body weight gain, due to the shorter gestation period, compared to those in the term group during the pregnancy (p=0.015), even though there were no significant differences in the weekly body weight gain in the second and third trimesters. For the neonates, gestational age, birth weight, body length and placental weight were significantly lower in the preterm group than in the term group. The ponderal index, which is, the body weight in kilograms divided by the cube of body height in meters, was not significantly different between groups. In addition, there was no significant difference in neonate gender between the preterm and term groups.

Dietary profiles for the mothers of preterm and term neonates in different trimesters are shown in Table 2. The results of food intake collected from 24-hr recall questionnaires did not include the amounts of supplements taken by the mothers. Using a mixed effects model, the differences in maternal nutrient intake between the preterm and term neonates, and among the three trimesters, were evaluated. Our results showed that cholesterol intake was 15 to 20% lower in the preterm group compared to the term group during the pregnancy. There were no significant differences in the intakes of other nutrients between the preterm and term groups. However, the intakes of total calories, protein, carbohydrates, fat, phosphorous, magnesium, and niacin as well as vitamins B-1, B-2, and B-6 were significantly affected by trimester, as intakes were significantly greater in the second and third trimesters compared to the first trimester. Vitamin E intake significantly increased in the third trimester compared to the first trimester. In addition, the intakes of zinc and potassium significantly increased in the second trimester compared to the first trimester and further increased in the third trimester.

The blood biochemical parameters for the mothers of preterm and term neonates in different trimesters and at delivery are shown in Table 3. The circulating numbers of WBC and serum concentrations of albumin were significantly lower and the serum concentrations of magnesium and ferritin were significantly greater in the preterm group compared to the term group (group effect, p< 0.05). The numbers of WBC, RBC, and platelet; the levels of hemoglobin and hematocrit; and the concentrations of albumin, total calcium, magnesium, iron and ferritin were significantly different during the pregnancy and at delivery (trimester effect, p<0.05). For example, WBC were significantly lower and platelets were significantly higher in the first trimester compared to the other trimesters and at delivery. RBC, hemoglobin, hematocrit and ferritin significantly decreased during the trimesters, but partially increased at delivery. Serum albumin, total calcium, and magnesium significantly decreased during the trimesters and further decreased at delivery. However, serum iron concentrations significantly decreased in the third trimester, while they tended to increase at delivery.

The correlations of maternal body weight gain during pregnancy, neonatal birth weight and length, and maternal nutrient intakes and blood biochemical parameters in different trimesters are shown in Table 4. There were significant positive correlations in maternal body weight gain with neonatal birth weight in all trimesters and with birth length in the first and second trimesters. In the three trimesters, the intakes of calories, protein, fat, cholesterol (r=0.236, 0.144, and 0.123 for the first, second, and third

Table 2. Daily energy, macronutrient, and micronutrient intake of mothers of preterm and term neonates in different trimesters[†]

	Term[‡]			Preterm[‡]			Mixed effect model		
	1st trimester	2nd trimester	3rd trimester	1st trimester	2nd trimester	3rd trimester	Group	Trimester	Interaction
Energy, kcal	1780±587[b§]	1996±640[a]	2097±618[a]	1602±738	1994±769	2128±896	0.552	<0.001	0.580
Protein, g	67.6±25.6[b]	77.0±27.0[a]	80.6±28.2[a]	61.7±25.5	77.8±34.7	76.7±27.2	0.407	0.003	0.726
Carbohydrate, g	231±79[b]	258±86[a]	272±85[a]	217±109	276±117	282±131	0.649	<0.001	0.527
Fat, g	67.3±30.2[b]	75.6±32.3[a]	79.0±31.6[a]	57.0±34.8	67.6±29.8	79.5±37.2	0.153	0.004	0.515
Cholesterol, mg	333±241[b]	370±215[a]	395±253[a]	259±161	270±171	354±231	0.020	0.092	0.696
Ca, mg	578±35 [b]	660±418[a]	700±413[a]	501±358	567±343	659±388	0.625	0.405	0.512
P, mg	964±372[b]	1104±404[a]	1158±428[a]	870±353	1047±426	1108±449	0.205	0.004	0.944
Mg, mg	225±96[b]	259±109[a]	272±109 [a]	217±92	269±184	280±119	0.812	0.006	0.856
Fe, mg	13.2±6.8[b]	15.5±8.6[a]	15.9±8.6[a]	13.4±8.9	13.7±7.4	15.1±7.2	0.418	0.198	0.799
Zn, mg	8.90±3.6[c]	10.0±3.8[b]	10.9±4.3[a]	9.6±9.0	10.5±5.0	10.8±4.8	0.512	0.052	0.844
K, mg	2173±923[c]	2503±1003[b]	2683±100 [a]	1963±909	2422±1091	2663±1185	0.424	<0.001	0.843
Vit B-1, mg	1.10±0.51[b]	1.24±0.56[a]	1.33±0.64[a]	1.05±0.62	1.38±0.64	1.24±0.60	0.983	0.029	0.345
Vit B-2, mg	1.28±0.71[b]	1.47±0.77[a]	1.59±0.79[a]	1.14±0.60	1.31±0.83	1.52±0.83	0.213	0.021	0.911
Vit B-6, mg	1.34±0.58[b]	1.58±0.65[a]	1.66±0.64[a]	1.22±0.63	1.70±1.02	1.62±0.68	0.897	<0.001	0.524
Vit B-12, μg	4.57±6.17	5.10±6.23	5.75±7.17	6.90±15.9	3.94±5.48	5.09±4.75	0.853	0.500	0.258
Niacin, mg	13.6±6.1[b]	15.7±6.8[a]	16.4±6.9[a]	13.2±7.3	16.0±8.1	15.7±6.8	0.746	0.031	0.887
Folate, μg	284±149[b]	327±173[a]	339±167[a]	304±143	299±190	364±228	0.800	0.079	0.513
Vit C, mg	114±96[b]	135±112[ab]	151±124[a]	126±120	123±101	152±123	0.982	0.174	0.813
Vit A, μg RE	643±1055	802±1026	832±1089	635±705	740±759	973±955	0.879	0.513	0.975
Vit E, mg α-TE	10.0±5.9[b]	10.9±7.3[ab]	11.1±5.3[a]	8.1±4.6	11.4±7.9	12.7±9.4	0.906	0.024	0.227

[†]Values are means±SD. Values for the mixed effects model are *p* values for the group effect, the trimester effect, and the interactions between group and trimester.
[‡] Sample sizes for the mixed effects model are 16 and 303 for preterm and term neonates, respectively.
[§]Significant differences of each parameters among the 3 trimesters are indicated by different superscript letters in the values of term neonates ($p<0.05$).

Table 3. Maternal blood biochemical parameters in preterm and term neonates in different trimesters and delivery[†]

	Term[‡]				Preterm[‡]				Mixed effect model		
	1st trimester	2nd trimester	3rd trimester	Delivery	1st trimester	2nd trimester	3rd trimester	Delivery	Group	Trimester	Interaction
WBC, $10^3/\mu L$	8.83±2.06^{b§}	9.47±2.18^{a}	9.73±2.21^{a}	9.54±2.22^{a}	7.64±1.58	8.47±1.66	8.35±1.18	9.41±1.86	<0.001	<0.001	0.192
RBC, $10^6/\mu L$	4.25±0.42^{a}	3.87±0.40^{c}	3.74±0.40^{d}	4.01±0.44^{b}	4.35±0.33	3.92±0.42	3.83±0.39	3.79±0.45	0.990	<0.001	0.021
Hb, g/dL	12.6±1.0^{a}	11.7±0.9^{b}	11.3±1.1^{c}	11.6±1.3^{b}	13.0±0.9	11.8±1.3	11.6±1.0	11.6±1.5	0.231	<0.001	0.431
HCT, %	36.9±2.6^{a}	34.3±2.5^{b}	33.3±2.9^{c}	34.4±3.6^{b}	38.6±2.8	34.3±3.9	34.0±2.9	33.7±4.4	0.436	<0.001	0.064
Platelet, $10^3/\mu L$	277±58^{a}	263±54^{b}	262±58^{b}	253±65^{b}	276±79	267±55	266±64	229±52	0.406	<0.001	0.401
Albumin, g/dL	4.23±0.24^{a}	3.90±0.22^{b}	3.64±0.22^{c}	3.20±0.29^{d}	4.24±0.20	3.76±0.52	3.64±0.21	2.98±0.33	0.001	<0.001	0.008
Total Ca, mg/dL	9.07±0.36^{a}	8.93±0.41^{b}	8.75±0.41^{c}	8.51±0.59^{d}	8.97±0.33	9.02±0.36	8.69±0.36	8.66±0.82	0.767	<0.001	0.534
Mg, mg/dL	2.11±0.14^{a}	1.95±0.14^{bc}	1.97±0.14^{b}	1.89±0.28^{c}	2.16±0.14	1.94±0.13	1.94±0.15	2.13±0.81	0.044	<0.001	0.008
Fe, mg/dL	85.9±36.4^{a}	83.4±34.2^{a}	69.4±42.2^{b}	72.2±43.8^{b}	88.2±24.3	78.5±27.6	67.4±23.7	85.1±38.4	0.208	0.013	0.495
Ferritin, ng/dL	58.3±48.2^{a}	37.6±32.5^{b}	14.3±14.1^{d}	24.0±36.9^{c}	60.7±41.3	46.6±38.0	16.7±15.2	36.0±30.0	0.031	<0.001	0.402

[†]Values are means ± SD. Values for the mixed effects model are *p* values for the group effect, the trimester effect, and the interactions between group and trimester. WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; HCT, hematocrit.
[‡]Sample sizes for the mixed effects model are 14 and 262 for preterm and term neonates, respectively.
[§]Significant differences of each parameter among the 3 trimesters and at delivery are indicated by different superscript letters in the values of term neonates ($p<0.05$).

Table 4. Correlations of body weight gain, birth weight and birth length with maternal nutrient intakes and blood biochemical parameters in all women[†]

	Body weight gain		Birth weight		Birth length	
	r	*p*	r	*p*	r	*p*
Body weight gain, kg						
1st trimester	---	---	0.195	<0.001	0.165	<0.001
2nd trimester	---	---	0.233	<0.001	0.179	<0.001
3rd trimester	---	---	0.125	0.008	0.045	0.343
Energy intake, kcal/d						
1st trimester	0.203	<0.001	0.146	0.009	0.11	0.049
2nd trimester	0.185	<0.001	0.087	0.079	0.053	0.282
3rd trimester	0.218	<0.001	0.073	0.142	0.105	0.036
Protein intake, g/d						
1st trimester	0.206	<0.001	0.134	0.017	0.103	0.066
2nd trimester	0.166	<0.001	0.097	0.049	0.065	0.188
3rd trimester	0.199	<0.001	0.138	0.006	0.169	<0.001
Fat intake, g/d						
1st trimester	0.193	<0.001	0.129	0.021	0.086	0.127
2nd trimester	0.141	0.004	0.078	0.114	0.047	0.346
3rd trimester	0.198	<0.001	0.061	0.224	0.099	0.047
Ca intake, mg/d						
1st trimester	0.041	0.468	0.077	0.168	0.096	0.087
2nd trimester	0.066	0.184	0.122	0.014	0.098	0.048
3rd trimester	0.147	0.003	0.105	0.036	0.153	0.002
P intake, mg/d						
1st trimester	0.198	<0.001	0.139	0.013	0.131	0.019
2nd trimester	0.148	0.003	0.118	0.017	0.099	0.046
3rd trimester	0.190	<0.001	0.127	0.011	0.184	<0.001
Mg intake, mg/d						
1st trimester	0.135	0.016	0.094	0.095	0.068	0.226
2nd trimester	0.118	0.017	0.023	0.639	0.009	0.86
3rd trimester	0.148	0.003	0.120	0.016	0.177	<0.001
Fe intake, mg/d						
1st trimester	0.134	0.017	0.060	0.287	0.093	0.096
2nd trimester	0.100	0.044	0.089	0.072	0.077	0.121
3rd trimester	0.105	0.035	0.112	0.025	0.149	0.003
Zn intake, mg/d						
1st trimester	0.131	0.019	-0.003	0.962	-0.019	0.729
2nd trimester	0.160	0.001	0.087	0.078	0.075	0.131
3rd trimester	0.149	0.003	0.112	0.025	0.126	0.012
Vit B-2 intake, mg/d						
1st trimester	0.163	0.004	0.124	0.027	0.143	0.011
2nd trimester	0.075	0.132	0.170	<0.001	0.112	0.024
3rd trimester	0.170	<0.001	0.086	0.085	0.138	0.006
Niacin intake, mg/d						
1st trimester	0.189	<0.001	0.086	0.126	0.094	0.094
2nd trimester	0.122	0.013	0.102	0.039	0.056	0.263
3rd trimester	0.174	<0.001	0.052	0.302	0.083	0.099
Vit C intake, mg/d						
1st trimester	0.179	0.001	0.017	0.756	0.090	0.110
2nd trimester	0.138	0.005	0.057	0.248	0.046	0.353
3rd trimester	0.103	0.039	-0.004	0.943	0.016	0.743
WBC, $10^3/\mu L$						
1st trimester	0.086	0.106	0.075	0.16	0.156	0.003
2nd trimester	0.123	0.029	0.155	0.006	0.131	0.02
3rd trimester	0.117	0.028	0.108	0.043	0.119	0.026
Delivery	0.044	0.384	-0.046	0.368	-0.045	0.371
Serum Fe, µg/dL						
1st trimester	0.026	0.664	-0.047	0.438	-0.067	0.271
2nd trimester	0.062	0.275	-0.05	0.375	-0.058	0.309
3rd trimester	-0.01	0.849	-0.111	0.041	-0.062	0.25
Delivery	-0.046	0.405	-0.111	0.042	-0.05	0.364
Ferritin, ng/dL						
1st trimester	-0.039	0.516	-0.001	0.991	-0.007	0.906
2nd trimester	-0.06	0.288	-0.102	0.071	-0.078	0.169
3rd trimester	-0.019	0.721	-0.071	0.188	-0.019	0.727
Delivery	-0.05	0.366	-0.138	0.012	-0.127	0.021

[†]Values are correlation coefficients (r) and *p*-values.

trimester, respectively), phosphorus, magnesium, iron, zinc, potassium (r=0.180, 0.165, and 0.205 for the first, second, and third trimester, respectively), vitamin B6 (r=0.200, 0.149, and 0.188 for the first, second, and third trimester, respectively), vitamin C, and niacin had significant positive impacts on maternal body weight gain (p <0.05). In addition, the intakes of folate (r=0.134) and vitamin B-1 (r=0.194), B-2, A (r=0.131), and E (r=0.192) in the first trimester; the intakes of carbohydrates (r=0.171) in the second trimesters; and the intakes of carbohydrates (r=0.175), calcium, folate (r=0.102), and vitamins B-1 (r=0.133), B-2, and E (r=0.182) in the third trimester were positively correlated with maternal body weight gain (p<0.05). We further evaluated the correlations of maternal body weight gain with blood biochemical parameters. We found that maternal body weight gain was positively correlated with WBC and hemoglobin in the second and third trimesters, positively correlated with hematocrit in the third trimester (r=0.104), and negatively correlated with serum magnesium at delivery (r= –0.158).

In the three trimesters, protein and phosphorus intakes have significant positive impacts on birth weights of neonates. In addition, the intakes of calories, fat, carbohydrate (r=0.124), and vitamin B-1 (r=0.126) and B-2 in the first trimester; the intakes of calcium, potassium (r=0.115), niacin, vitamins B-2 and B-12 (r=0.103) in the second trimester; and the intakes of calcium, magnesium, iron, zinc and potassium (r=0.120) in the third trimester were positively correlated with birth weights of neonates (p<0.05). In addition, WBC in the second and third trimesters and RBC (r=0.122) and albumin (r=0.132) at delivery were positively correlated with neonatal birth weight. However, serum ferritin at delivery, and serum iron in the third trimester and at delivery, were negatively correlated with neonatal birth weight.

For birth length of the neonates, phosphorus and vitamin B2 intakes were the factors that had significant positive impacts in all of the three trimesters. The intake of calories in the first trimester; the intakes of calcium and vitamin B-12 (r=0.132) in the second trimester; and the intakes of calories, fat, cholesterol (r=0.141), calcium, magnesium, iron, zinc, potassium (r=0.149), and vitamin E (r=0.106) in the third trimester were positively correlated with birth length of neonates (p<0.05). Additionally, WBC was the only factor to have significantly positive impacts in all three gestational trimesters, but not at delivery. In addition, RBC (r=0.134), hematocrit (r=0.105), serum albumin (r=0.172), and serum calcium (r=0.111) were positively correlated, and serum ferritin was negatively correlated, with neonatal birth length at delivery.

DISCUSSION

The causes and mechanisms of preterm delivery are not completely understood; therefore, the high morbidity and mortality of preterm neonates are still a challenge faced by pediatricians.[2] The fundamental approach to solve these problems may start with having a successful pregnancy. It has been indicated that maternal preconception weight, total weight gain and maternal nutrient intake during pregnancy, especially protein and micronutrients, are significantly associated with spontaneous preterm delivery in the USA and Europe.[3-5,7] However, there is little information regarding nutrient intake and preterm delivery in Taiwanese women. In the present study, we showed that maternal weight gain in early pregnancy and circulating WBC, mineral intake, protein status, and iron status in late pregnancy are useful markers to predict poor nutrition and preterm delivery in Taiwanese women.

In prenatal care, the easiest way to monitor pregnancy status is body weight measurement. Inadequate weight gain in late pregnancy is closely associated with low body weight and BMI before pregnancy and an increased risk of preterm delivery.[3-5] In the present study, Taiwanese women with preterm delivery had significantly lower total body weight gain (due to early delivery) and lower circulating WBC compared to those with term delivery, as was also shown in German women with preterm delivery.[19] In addition, the weekly maternal weight gain in the preterm group was significantly lower than in the term group in the first trimester and was positively correlated with neonatal birth weight and birth length in the first and second trimesters. The results of total and weekly maternal weight gain indicated that the maternal weight gain in the first trimester plays an important role in affecting the pregnancy outcome. Moreover, circulating WBC were positively correlated with maternal weight gain, neonatal birth weight and birth length in the second and third semesters. These results indicated that maternal weight gain in early pregnancy and immune function in later pregnancy play crucial roles in determining birth outcomes. These findings are different from observations in western countries.[3-5] These inconsistent results might be due, at least partly, to the fact that many Taiwanese women may consume folk medicinal foods, especially in late pregnancy. This traditional custom may compensate for low body weight gain of early pregnancy.

It was shown that neonates had significantly lower birth weights, birth lengths, and head circumferences from women who suffered from food deficiencies in the third trimester compared to women who had adequate food intake.[22] According to a study by Edison *et al.*,[23] low maternal serum cholesterol was strongly associated with preterm delivery because maternal cholesterol is essential for both hormonal and physical changes during early pregnancy.[24,25] In this study, we found that maternal cholesterol intake was approximately 20% lower in the preterm group compared to the term group during pregnancy and was positively correlated with maternal weight gain. Additionally, the intakes of calories, protein and fat had significantly positive impacts on maternal weight gain in all three trimesters, on neonatal birth weight in the first trimester, and on neonatal birth length in the third trimester. Among the nutrients examined, only protein and phosphorus intakes had positive correlations with neonatal birth weight, during pregnancy (p<0.05). These correlations might explain significant low serum albumin in the preterm group compared to the term group.

In the present study, there were no significant differences in maternal intakes of water- and fat-soluble vitamins between women with preterm and term delivery (Table 2). These results revealed that the intakes of energy and protein metabolism-associated vitamins, such as B-1, B-2, niacin and B6, may be altered during pregnancy. Maternal intakes of vitamin C and B complex, except B-

12, were positively correlated with maternal weight gain, and the intake of vitamin B-2 was positively correlated with neonatal birth weight and length during pregnancy (Table 4). Intakes of fat-soluble vitamins, including vitamin A and E were positively correlated with maternal weight gain but not with neonatal birth weight. There is little information regarding the vitamin status of pregnant women in different trimesters in Taiwan, and we did not measure serum biomarkers of these vitamins. Further studies may address biomarkers of different vitamins to establish a precise database for pregnant women.

Evidence showed that even with adequate energy and protein intakes, variations in mineral intakes may affect birth weight.[7] Villar *et al*. indicated that teenager mothers supplemented with 2 g/d of calcium may effectively decrease the incidence of preterm delivery from 21.1% to 7.4%.[26] In addition, iron-deficiency anemia is associated with low energy and iron intakes in early pregnancy that increased the risk of preterm delivery.[27] In the present study, we found that maternal iron intake positively correlated with maternal weight gain, neonatal birth weight and birth length in the third trimester ($p<0.05$, Table 4); however, the intakes of calcium and iron did not increased during pregnancy and were not significantly different between women with preterm and term delivery. We also observed that maternal serum iron and ferritin gradually decreased from the first trimester to the third trimester and that serum ferritin was significantly higher in women with preterm delivery than those with term delivery (Table 3). In particular, maternal serum iron was negatively correlated with neonatal birth weight in the third trimester and serum ferritin was negatively correlated with neonatal birth weight and length in the third trimester and at delivery (Table 4). Decreased serum iron and ferritin may be due to increased maternal blood volume that diluted maternal serum iron and ferritin in late pregnancy. However, the greater serum ferritin in women with preterm delivery might be related to iron and folate deficiency in early pregnancy or to recent infection, as suggested by Scholl and Hediger.[28]

It has been demonstrated that severe zinc deficiency may lead to fetal abnormalities, miscarriage and fetal growth retardation[7,29] and that low zinc status is associated with low birth weight.[30] However, the results of studies examining zinc supplementation in pregnancy outcomes are not consistent.[13,29,30] In this study, maternal zinc and magnesium intakes were not significantly different between the women with preterm and term delivery, but they were positively correlated with maternal weight gain and neonatal birth weight and length in the third trimester. Magnesium is an important cofactor for enzymatic reactions and plays an important role in neurochemical transmission and muscular excitability. It has been reported that low magnesium intake may result in hypomagnesemia (magnesium 1.4 mg/dl or less) and may increase contractions of the uterus, leading to preterm delivery.[17,18,29] As shown in several studies, magnesium supplementation started in early pregnancy appears promising in preventing preterm delivery and in increasing birth weight.[11,12,31] In contrast, Taiwanese women with preterm delivery had greater serum magnesium than those with term delivery. Similar contradictions were found in the maternal serum magnesium and maternal weight gain at delivery. The increase of maternal serum magnesium in the preterm group might have resulted from the use of $MgSO_4$ to prevent uterine contractions during preterm labor control.[32]

In conclusion, our results showed that the incidence of preterm delivery was lower in Taiwan compared to western countries. In addition, maternal weight gain during pregnancy, especially in the first trimester, was associated with preterm delivery. The results of a mixed effects model revealed that maternal cholesterol intake was approximately 20% lower and that immune function (WBC counts) and protein nutrition status (serum albumin) were significantly lower in mothers with preterm delivery compared to those with term delivery. In contrast, gradual decrease in serum magnesium and ferritin concentrations during pregnancy were significantly reversed at delivery in mothers with preterm delivery. Moreover, maternal weight gain was positively correlated with caloric and mineral intakes, and neonatal birth weight was positively correlated with maternal weight gain and intakes of protein and minerals, especially calcium, magnesium, iron and zinc in late pregnancy. Taken together, our results indicated that low white blood cell counts and high serum ferritin concentrations in late pregnancy are useful markers to reveal poor nutrition status and an increased risk of preterm delivery in Taiwanese women.

ACKNOWLEDGEMENTS

We would like to thank all of the interviewers and all of the individuals who assisted with the survey in the hospital. This work is supported by the Department of Health, Executive Yuan, the Republic of China under the grant number DOH-94-TD-F-113-071 and DOH-95-TD-F-113-043.

AUTHOR DISCLOSURES

The authors have no conflict of interest.

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Original Article

Low body weight gain, low white blood cell count and high serum ferritin as markers of poor nutrition and increased risk for preterm delivery

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低體重增加、低白血球計數和高血清鐵蛋白可做為較差營養狀況的標記及增加早產的風險

本研究為探討影響臺灣產婦早產發生的因素。以到醫院產檢，懷孕 8-12 週的健康孕婦為對象，共收案 520 名，平均年齡 29.1±4.2 歲。分別在懷孕第一期、第二期與第三期，收集其基本資料和血液，進行體位測量和以 24 小時回憶法收集飲食資料。並在其生產時，收集母親的血液和體位資料與新生兒臨床資料。總計 53.7%為初產婦，早產率為 6.2%。早產組懷孕第一期體重增加和孕期體重增加總重，明顯低於足月組(p<0.05)。早產組母親膽固醇攝取量、白血球數、血清白蛋白顯著低於足月組(p<0.05)；而血清鎂和血鐵蛋白則顯著高於足月組(p<0.05)。產婦孕期體重增加總重與熱量和營養素攝取有顯著正相關(p<0.05)。新生兒出生體重與母親各孕期體重增加和蛋白質及磷攝取量有顯著正相關(p<0.05)；並與母親第一期熱量、維生素 B-1 和 B-2 攝取量及第三期鈣、鎂、鐵和鋅攝取量、白血球數有顯著正相關(p<0.05)。然而新生兒出生體重與母親第三期血清鐵和生產時血鐵蛋白呈現負相關(p<0.05)。總結而論，母親懷孕早期體重增加、白血球數與礦物質攝取量和懷孕晚期血鐵狀況可能為影響懷孕結果的主要因素。

關鍵字：營養素攝取、孕期體重增加、白血球數、血鐵蛋白、早產