Original Article

Impact of Periconceptional Multi-micronutrient Supplementation on Gestation: A Population-based Study[*]

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Abstract

Objective To examine the effect of periconceptional multi-micronutrient supplementation on gestation and birth outcomes.

Methods A population-based community intervention program was conducted in 18 counties in China. Participants were divided into an intervention group, who received multi-micronutrient supplementation from at least 3 months before pregnancy throughout the first trimester, and a control group. Pregnant women were followed up to record information about birth outcomes. Maternal socio-economic characteristics and main birth outcomes were evaluated. Gestational age was further analyzed using survival analysis, to determine the time distribution of delivery.

Results Periconceptional multi-micronutrient supplementation was associated with higher birth weight, birth length and occipitofrontal head circumference, and with lower incidence rates for stillbirth, low birth weight, and preterm birth. Moreover, periconceptional multi-micronutrient supplementation changed the time distribution of delivery, making the deliveries more clustered in the period between day 275 and day 295 of gestation.

Conclusion Our study shows that periconceptional multi-micronutrient supplementation is beneficial for fetal development and optimizes all measured aspects of health in neonates in socioeconomically disadvantaged areas in China. The change in time distribution of deliveries caused by multi-micronutrient supplementation needs further clarification.

Key words: Multi-micronutrient Supplementation; Gestation; Birth weight; Gestational age

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INTRODUCTION

A healthy nutritional status before and during pregnancy is important for achieving a healthy pregnancy outcome[1]. More than 20 years ago, Smithells et al. first reported that pregnant women with micronutrient-deficient diets were more prone to having babies with neural tube defects (NTDs)[2]. Since then, numerous double-blind, randomized trials have confirmed that using folic acid or multi-micronutrient supplements containing folic acid during the periconceptional period leads to a four-fold reduction in the risk of NTDs[3]. Additionally, several studies have illustrated the beneficial effects of multi-micronutrient supplementation during

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pregnancy on other adverse pregnancy outcomes such as low birth weight, small-for-gestational-age births, preterm birth, stillbirths, and perinatal and neonatal mortality[4-5]. As research accumulated, the beneficial effect of multi-micronutrient supplementation on these birth outcomes became accepted[6-7]. What is controversial, yet less discussed, is the effect of multi-micronutrient supplementation on gestational age, an important index associated with all birth outcomes.

A recently updated meta-analysis showed a significant reduction in the risk of low birth weight and a significant increase birth weight in infants born to women who received multi-micronutrients supplementation during pregnancy, in comparison with placebo[6]. However, there was no significant effect of multi-micronutrient supplementation on the risk of preterm or small-for-gestational-age births. Furthermore, no significant difference in gestational age was found. It may be interesting to note that preterm and small-for-gestational-age births are both related to the duration of gestation. This reminds us that gestational age is an important confounding factor. Yet, as far as we know, all previous studies simply averaged gestational age and none showed the actual time distribution of deliveries.

The aim of our study was to examine the effects of periconceptional multi-micronutrient supplementation on adverse birth outcomes. More importantly, the effect of multi-micronutrient supplementation on the time distribution of delivery was examined by survival analysis method.

MATERIALS AND METHODS

Study Design

All data were obtained from the community nutritional intervention study authorized by the National Population and Family Planning Commission. The study design was approved by the ethics committee of Peking University Health Science Center. The study was conducted in Henan, Guizhou, Hunan, and Jilin provinces, including ten counties in the interventional group, and eight counties in the control group. All counties form both groups were selected by systematic random sampling and were matched by economic status and ethnical structure. Female residents who were at least 18 years old, not pregnant but planned to get pregnant in the next six months, and who agreed to undergo the follow-up interviews were included. All eligible participants were informed on the details of the intervention program and were asked to provide written informed consent at the first interview.

Participants in the counties from the intervention group were supplied with multi-micronutrient capsules (Forceva, Unigreg Ltd, Morden, UK). Supplementation was started at the first interview at least three months before pregnancy, and continued throughout the first trimester. The capsules were distributed each month and participants were asked to take one capsule a day, after a meal. The multi-micronutrient capsules were plate packaged with 30 capsules in one box (two plates, about 44 g), which was nearly a monthly dose. Each capsule contained 23 vitamins and micronutrients, including 400 μg folic acid, 563 IU vitamin A, 200 IU vitamin D_2, 1.4 mg vitamin B_1, 1.4 mg vitamin B_2, 3 μg vitamin B_{12}, 60 mg vitamin C, 8 mg vitamin E, 100 μg biotin, 14 mg niacinamide, 4 mg pantothenic acid, 100 mg calcium, 10 mg iron, 2 mg cuprum, 10 mg zinc, 77 mg phosphorus, 30 mg magnesium, 3 mg manganese, 30 μg selenium, 100 μg molybdenum, and 4 mg potassium. Start and end days of supplementation were recorded for every participant in the intervention group. All participants in the intervention group were followed up monthly to ensure compliance. Compliance was expressed as the number of days of supplementation before and after the last menstrual period. Participants in the control group were given no nutrient intervention but recorded any nutrient supplementation and dosage used during the study period.

All participants were interviewed using a prepared standard questionnaire that included questions regarding socioeconomic status, daily environmental factors, lifestyle related behavior factors and medical history. All participants were followed up monthly to record the conditions of pregnancy and birth outcomes. The date of the start of the last menstrual cycle and the date of delivery were recorded and used to calculate gestational age. All birth outcomes were recorded, including spontaneous abortion, induced abortion, fetal death, stillbirth, and live birth. We recorded and photographed neonates with detected malformations, which were diagnostically confirmed by consulting qualified pediatric doctors.

Measurements and Statistical Analysis

Individuals with 28 weeks of pregnancy and confirmed pregnancy outcomes were included in our analysis. Birth weight was measured by hospital staff within 72 h of delivery. Birth weight was measured with an electronic scale with precision to the nearest 1 g. Birth length was measured to the nearest 1 cm with a portable measuring board with fixed head piece. Occipitofrontal head circumference was measured with a measuring tape to the nearest 1 cm. Gestational age was calculated based on the first day of the last menstrual period, as obtained at the baseline interviews. Low birth weight was defined as <2500 g. Preterm delivery was defined as delivery before 37 completed weeks of gestation.

Differences in baseline demographic and socio-economic characteristics between groups were examined with Student's *t*-tests or chi-square (χ^2) tests. Differences in birth outcomes between the two groups, including gestational age, mode of delivery, number of births, gender, stillbirths, and malformations were also examined. Only live infants without detectable malformations were included in the analyses of low birth weight, preterm birth and birth anthropometry, which included birth weight, birth length, and occipitofrontal head circumference. Mean differences and 95% confidence intervals were estimated for birth weight, birth length, occipitofrontal head circumference, and gestational age. P-values were calculated with analyses of covariance, adjusted for confounders.

Survival analysis was used to compare the time distribution of gestational ages between the two groups and survival curves were drafted to demonstrate the time distribution of delivery. We stratified the data by potential confounders to eliminate their interference. Last, we compiled a “life table” to quantitatively analyze the time distribution of delivery. All statistical analyses were performed with the SAS 9.2 software.

RESULTS

The study cohort included 60 720 women by systematic random sampling. In total, 52 043 women completed follow-up with good compliance, 28 weeks of pregnancy and confirmed pregnancy outcomes. Among these, 25 444 (48.89%) women received the nutrient supplementation intervention. The rate of loss to follow-up was 14.29%.

Table 1 presents maternal demographic characteristics, socio-economic status, medical history, dietary habits and other life factors. The average age of the women was 24.9 years in the control group and 25.4 years in the intervention group. About 97% were of Han ethnicity. About 85% had an education level of junior high school or higher. More than 80% were farmers. More than 80% considered themselves to be of moderate economic status. Women in the intervention group were less prone to be exposed to passive smoking, drink alcohol and drink tea, yet they consumed less green vegetables and fruits.

There was good compliance to the multi-micronutrient supplementation intervention in the intervention group. The mean number of days of supplementation was 149.8±42.4. The number of days of supplementation before the last menstrual period was 49.3±55.1, and after the last menstrual was 99.7±41.6. Of the participants, 38.2% took the multi-micronutrient capsules for more than 30 days before the last menstrual period, and 79.4% took the multi-micronutrient capsules for more than 90 days after the last menstrual period.

Pregnancy outcomes and anthropometrics are shown in Table 2 and Table 3. The rates of stillbirths, malformations, and low birth weight were significantly lower in the intervention group than in the control group. Because the rate of preterm births was calculated from live births without detectable malformations, the rate of preterm births was similar between the two groups. Moreover, among the live births without detectable malformations, mean birth weight, birth length, and occipitofrontal head circumference of the neonates in the intervention group were all significantly higher than in the control group. The mean gestational age in the interventional group was 0.6 days longer than that of the control group.

Kaplan-Meier survival analysis was used to compare the time distributions of live births without detectable malformations in the two groups. Delivery time distribution was significantly altered by the intervention, with a χ^2 *P*-value of <0.001. The curve plots show that deliveries were clustered in different time intervals for each group (Figure 1). Using the life table method, we calculated the possibility of delivery completed at and before a certain gestational age between two groups (Table 4). Through comparing the chance of delivery in the two groups, we detected two time points that divided gestation into three phases: day 275 and day 295. Before day 275, the chance of delivery was higher in the control group than in the intervention group; between day 275 and day 295, the chance of delivery in the intervention group was higher; after day 295, the chance of delivery was higher again in the control group. In other words, deliveries in the intervention group were more clustered between days 275 and 295 than those of the control group (Table 5).

Table 1. Maternal Demographic Characteristics, Social-economic Status, Medical History, and Environmental Risk Exposures

		Control Group		**Intervention Group**		***t*/X^2 Value**	***P*-value**
		***n*=26 599**		***n*=25 444**			
Age of Women during Pregnancy		24.87	±3.79	25.39	±3.94	-15.13	<.0001
Age of Husbands at Time of Pregnancy		26.45	±3.85	26.92	±3.87	-14.07	<.0001
Province	Jilin	5202	19.56%	5468	21.49%	146.08	<.0001
	Henan	7357	27.66%	7516	29.54%		
	Guizhou	6401	24.07%	6303	24.77%		
	Hunan	7630	28.69%	6157	24.20%		
Ethnicity	Han	25 977	97.67%	24 501	96.31%	96.15	<.0001
	Other	582	2.33%	943	3.69%		
Education	Primary school	3767	14.16%	3875	15.23%	100.25	<.0001
	Junior high school	20 574	77.35%	18 827	73.99%		
	Senior high school or above	2258	8.49%	2742	10.78%		
Occupation	Farmer	22 182	83.39%	21 045	82.71%	4.31	0.0378
	Other	4417	16.61%	4399	17.29%		
Economic Status	Well	2838	10.67%	2667	10.49%	30.48	<.0001
	Moderate	2 2072	83.00%	21 435	84.29%		
	Bad	1684	6.33%	1329	5.23%		
Passive Smoking	No	11 167	42.00%	15 457	60.75%	1830.27	<.0001
	Yes	15 423	58.00%	9986	39.25%		
Drinking Alcohol	No	26 226	98.67%	25 220	99.13%	24.68	<.0001
	Yes	353	1.33%	222	0.87%		
Drinking Tea	No	15 865	59.66%	19 866	78.08%	2051.57	<.0001
	Yes	10 728	40.34%	5576	21.92%		
Diet (times/week)	Green vegetables	6.55	±1.26	6.49	±1.24	5.88	<.0001
	Bean products	5.04	±2.40	5.17	±2.20	-6.59	<.0001
	Fruits	5.54	±2.27	5.5	±2.18	1.66	0.0969

Note. Data are expressed as either the mean±SD or the number of cases and the percentage of the total number of subjects in the group.

Table 2. Pregnancy Outcomes

		Control Group *n*=26 599		Intervention Group *n*=25 444		Chi-square Value	*P*-value
Parity	1	18 496	69.54%	17 732	69.70%	39.43	<.0001
	2	6 111	22.98%	6 122	24.07%		
	3	1 477	5.55%	1 216	4.78%		
	≥4	514	1.93%	369	1.45%		
Mode of Delivery	Natural childbirth	25 001	93.99%	23 288	91.53%	118.16	<.0001
	Cesarean section	1 095	4.12%	1 483	5.83%		
	Others	503	1.89%	673	2.65%		
Number of Births	Singleton	26 280	98.83%	25 233	99.18%	18.26	0.0001
	Twins	308	1.16%	202	0.79%		
	Triplets	4	0.02%	6	0.02%		
Neonate Gender	Male	14 358	53.99%	13 935	54.80%	3.34	0.065
	Female	12 222	45.96%	11 483	45.16%		
Birth Outcome	Live birth	26 186	98.45%	25 266	99.30%	84.30	<.0001
	Stillbirth	413	1.55%	178	0.70%		
Malformation	No	26 393	99.30%	25 364	99.77%	60.62	<.0001
	yes	186	0.70%	59	0.23%		
Low Birth Weight (<2500 g)[a]	No	25 843	99.16%	25 111	99.61%	41.07	<.0001
	yes	218	0.84%	99	0.39%		
Preterm Birth (<37 weeks)[a]	No	25 909	99.42%	25 088	99.52%	2.38	0.1231
	yes	152	0.58%	122	0.48%		

Note. Data are expressed as the number of cases and the percentage of the total number of subjects in the group. [a]Calculated from healthy births, excluding stillbirths and malformations.

Table 3. Neonate Anthropometrics

	Control Group *n*=26 599	Intervention Group *n*=25 444	*t*-value	*P*-value
Gestation (day)	274.5±15.0	275.1±14.8	-4.69	<.0001
Birth Weight (g)	3419.6±399.4	3435.2±386.7	-4.50	<.0001
Birth Length (cm)	49.9±3.1	50.0±3.0	-4.24	<.0001
Head Circumference (cm)	32.9±2.1	33.1±2.0	-8.32	<.0001

Note. Values are expressed as mean±SD. All values were calculated from healthy births, excluding stillbirths and malformations.

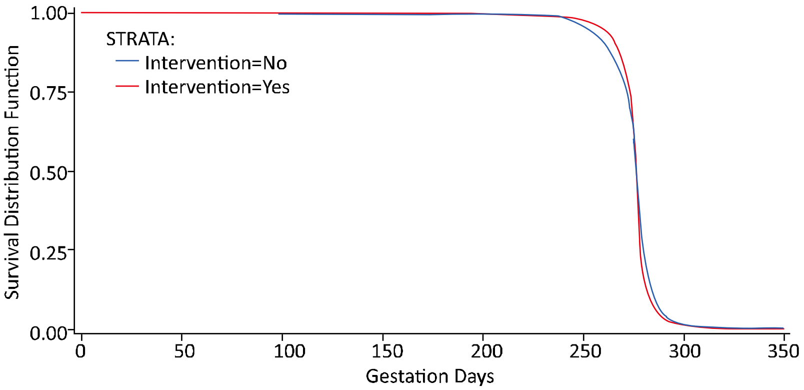

Figure 1. Delivery time distribution curves of the control and intervention groups. "Survival probability" in this figure indicates the probability of the pregnancy continuing (that is, the delivery does not happen). In the intervention group, deliveries tended to be clustered between day 275 and day 295 of gestation. Only live births without detectable malformations were included.

Table 4. Delivery Time Distribution Function Estimates between Control and Intervention Groups (from Gestational Day 250 to 310)

Gestational Day	Control Group		Intervention Group		Difference[c]
	Cumulative Probability[a]	Probability[b]	Cumulative Probability	Probability	
250	0.045176	0.018116266	0.025062	0.008628027	0.020114
255	0.062793	0.018450521	0.032758	0.007893835	0.030035
260	0.088538	0.027469919	0.047519	0.015260917	0.041019
265	0.134319	0.050228095	0.081462	0.035636406	0.052857
270	0.204559	0.081138433	0.146466	0.070768983	0.058093
275	0.344208	0.175561732	0.303469	0.183944635	0.040739
280	0.719681	0.572548918	0.790859	0.699739136	-0.071178
285	0.879480	0.570061252	0.923393	0.633706447	-0.043913
290	0.944314	0.537952207	0.960690	0.486861514	-0.016376
295	0.971911	0.495582373	0.974504	0.351411854	-0.002593
300	0.983101	0.398376589	0.982082	0.297223094	0.001019
310	0.988092	0.295342920	0.987173	0.284127693	0.000919

Note. [a]Cumulative probability of delivery at and before the gestational age. [b]Probability of delivery at the gestational age interval. [c]Difference in the cumulative probability of delivery between control and intervention groups.

Table 5. Delivery Time Distribution

	Control Group		Intervention Group		χ^2 Value	*P*-value
<275 days	9 252	(-34.78%)	7 796	(-30.64%)		
275-295 days	16 604	(-62.42%)	17 002	(-66.82%)		
>295 days	743	(-2.79%)	646	(-2.54%)		
Total	26 599	(-100.00%)	25 444	(-100.00%)	110.2597	<.0001

Note. Values are expressed as *n* (% of total).

When stratified by possible confounders such as province, ethnicity, education, occupation, economic status or passive smoking, this disparity still existed. Moreover, the disparity was more significant in strata with more risk exposure. For example, when stratified by passive smoking, the disparity was more pronounced in the stratum exposed to passive smoking (log-rank χ^2=64.6989, P<0.0001), yet less pronounced in the stratum without passive smoking (log-rank χ^2=39.97651, P<0.0001) (Figure 2). This inconsistency among strata also existed when stratified by education, occupation, economic status etc.

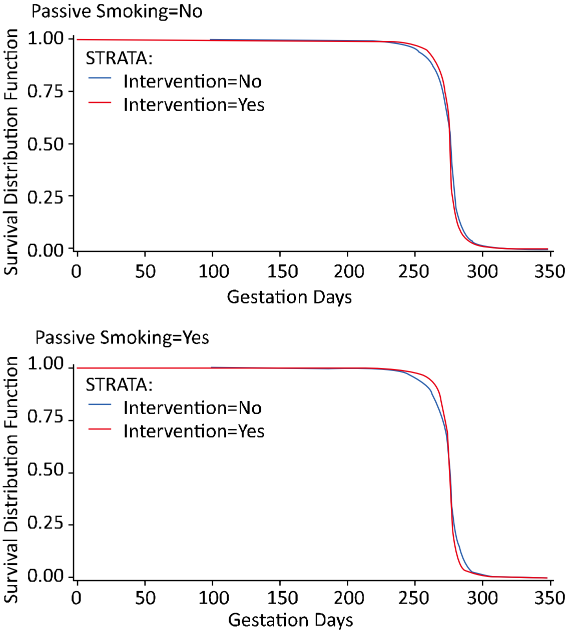

Figure 2. Delivery time distribution curves of the control and intervention groups stratified by passive smoking. "Survival probability" in this figure indicates the probability of the pregnancy continuing (i.e., the delivery does not happen). The difference between the control and intervention groups is more pronounced in stratum with passive smoking (Log-rank χ^2=64.6989, P<0.0001) than in stratum without passive smoking (Log-rank χ^2=39.97651, P<0.0001). The same effect was seen when stratified by education, occupation, or economic status. Only live births without detectable malformations were included.

DISCUSSION

Pregnancy requires increased intakes of both macro and micronutrients. A healthy nutritional status of a woman before and during pregnancy is important for a healthy pregnancy outcome[1]. Inadequate dietary intakes without any supplementation before and during pregnancy can lead to adverse birth outcomes, such as NTDs, low birth weight, small-for-gestational-age births, preterm birth, stillbirth, and perinatal and neonatal mortality. To improve a pregnant women's nutritional status, many nutritional interventions have been proposed, including supplementation with multi-micronutrients, calcium, zinc or folic acid, or balanced protein energy[8]. Some of these interventions are universally recommended for all women while some are proposed specifically in the context of the nutritional status of mothers, which may vary in different populations[9-13]. In our study, a multi-micronutrient supplementation intervention was examined for its effects on adverse birth outcomes.

We previously confirmed the preventive effect of periconceptional multi-micronutrient supplementation against NTDs[14]. Our previous study also showed that multi-micronutrient supplements reduced the incidence of stillbirth. In a recently published meta-analysis, it was suggested that the decrease in stillbirths could be explained by a decrease in NTDs[6]. Another study indicated that reduced neonatal mortality may be associated with the iron in the supplements, possibly mediated by increased gestational age and lower rates of preterm delivery[15]. As it is difficult to distinguish between stillbirths caused by NTDs and those caused by other conditions, we can only conclude that periconceptional multi-micronutrient supplementation lowers the risk of stillbirth caused by any condition, including NTDs.

In agreement with previous studies, our present results show that birth weight, birth length, and neonatal occipitofrontal head circumference were significantly increased in the multi-micronutrient supplementation group[6-7,9,15]. A previous study attributed this to improved intrauterine growth and prolonged gestational age[15]. In our study, the incidence rate of preterm birth was not different between two groups. This may be because we limited pregnancy more than 28 weeks and preterm birth rate was calculated from live births without detectable malformations, as most babies with malformations were stillborn or preterm.

In our study, multi-micronutrient supplementation was associated with significantly increased gestational age (0.6 days) compared with the control group. As most researchers had suggested, this appeared to be related to the reduction of early preterm deliveries, and therefore partly contributed to the decrease in neonatal mortality and the improvement in neonatal anthropometrics[6,15]. Many studies had indicated that preterm infants have much higher neonatal mortality than those born at term[16-17]. A study of birth outcomes among low birth weight infants reported that 75% of neonatal deaths were related to preterm delivery[17]. These findings strongly suggest that the increased gestational age and reduced risk of preterm delivery after multi-micronutrient supplementation may contribute to a decrease in neonatal mortality.

It could be speculated that the decrease in stillbirth and neonatal mortality was mainly the result of improved intrauterine growth, as represented by the increased birth weight and other neonatal anthropometrics. And the improved intrauterine growth was caused by the increased gestational age. All conditions in this causal path were improved by micronutrient supplementation. This causal pathway had been suggested by most of relative studies[15-17], yet none of them had shown in details how micronutrient supplementation changed gestational age.

Survival analysis coupled with delivery time distribution curves showed that deliveries in the intervention group were clustered in a certain time interval. As we calculated the probability of delivery at and before certain gestational ages in both groups, it was clear that in the intervention group more deliveries occurred between day 275 and day 295, which is the normal delivery time interval. This difference in time distribution between the two groups remained when data were stratified by possible confounders such as province, ethnicity, education, occupation, and economic status. Moreover, the difference between the two groups was more significant in strata with higher risk exposure. This demonstrates that the gestational age may be not necessarily increased or decreased by multi-micronutrient supplementation, but that the whole gestation and delivery time distribution may have been changed. A possible explanation could be that improved nutrient supply did improve fetal growth and therefore shortened the length of gestation. At the same time, improved nutrient supply also reduced the risk of preterm birth, making the time distribution more focused between days 275 and 295 of gestation. With this explanation, the interrelationship among preterm birth, birth weight and gestation age is much better explained. It may also help explain why in most studies with reduced incidence of preterm births caused by multi-micronutrient supplementation, gestation was neither shortened nor prolonged.

Our study was a population-based intervention trial designed to have a balanced distribution of confounders between groups though randomization by county clusters. The sample size was adequately powerful to detect small differences in any index. Population recruitment allowed complete tracing of fetal losses, including spontaneous and induced abortions and stillbirths, and pregnancy outcomes from both hospital and home deliveries. We used appropriate statistical methods in data analysis, especially the survival analysis for gestation age, which help us detect the novel finding of the more clustered delivery time distribution in the intervention group. All these ensured the reliability of our results.

In conclusion, our study showed that periconceptional multi-micronutrient supplements have significant health benefits for neonates, and may lower the risk of NTDs and stillbirths and increase birth weight, birth length and gestation age. Furthermore, the time distribution of deliveries in the intervention group was more concentrated in the interval between days 275 and 295 of gestation, which is the normal range for healthy, term deliveries. This change in delivery time distribution caused by multi-micronutrient supplementation is worth further investigation.

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