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The effect of vitamin B12 level on fetal birth weight

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Abstract

Objective: Vitamin B12 is a co-enzyme necessary for lipid, protein, carbohydrate metabolism, erythropoiesis, DNA and RNA synthesis and homocysteine metabolism. In this study, we aimed to investigate the effect of serum vitamin B12 level on birth weight in pregnant women.

Methods: This cross-sectional clinical study included a total of 463 cases who referred to our clinic for the gestational follow-up between 28 and 32 weeks of gestation. Pregnant women who were vegetarian or had systemic disease which may cause vitamin B12 deficiency or those with the history of delivering baby with neural tube defect were excluded from the study. The cases underwent venous blood sampling and their vitamin B12 levels were determined in biochemistry laboratory by Beckman Coulter device. Normal ranges of vitamin B12 levels were considered to be between 145 and 912 pg/ml. Statistical analysis of the data obtained from the study was carried out by SPSS version 16.0. Conformity of the data to normal distribution was evaluated by Shapiro-Wilk test. The data showing normal distribution were analyzed by using parametric tests.

Results: Mean vitamin B12 levels of the cases was 219±202 pg/ml and 169 cases (36.5%) had vitamin B12 deficiency. In terms of birth weights, mean weight was 3298±482 g in cases with low vitamin B12 levels while it was 3316±434 g in the cases with normal levels of vitamin B12 (p=0.288). When birth weights were distributed into the percentiles according to the weeks of gestation, it was seen that 39 cases (9.8%) were below 10th percentile, 333 cases (83.2%) were between 10th and 90th percentile, and 28 cases (7%) were above 90th percentile. According to these results, there was no significant difference between two groups in terms of birth weights.

Conclusion: According to the results of our study, there is statistically no significant effect of vitamin B12 level on birth weight and week of gestation.

Keywords: Gestation, vitamin B12 deficiency, birth weight.

Özet: Vitamin B12 düzeyinin fetal doğum ağırlığı üzerine etkisi

Amaç: Vitamin B12, lipid, protein, karbonhidrat metabolizması, eritropoez, DNA ve RNA sentezi ve homosistein metabolizması için gerekli olan bir ko-enzimdir. Bu çalışmada gebelerde serum vitamin B12 düzeyinin doğum ağırlığı üzerine olan etkisini incelemeyi amaçladık.

Yöntem: Bu kesitsel, klinik çalışmaya kliniğimizin gebe polikliniğine 28–32. gebelik haftaları arasında gebelik takibi için başvuran toplam 463 olgu dâhil edildi. Vejeteryan, vitamin B12 eksikliğine neden olabilecek sistemik hastalık veya nöral tüp defektli bebek doğurma öyküsü olan gebeler çalışma dışı bırakıldı. Olgulardan venöz kan örneklemesi yapılarak biyokimya laboratuvarında Beckman Coulter cihazı ile vitamin B12 düzeyi belirlendi. Vitamin B12 düzeyinin normal sınırları 145–912 pg/ml olarak kabul edildi. Çalışma sonucunda elde edilen verilerin istatistiksel analizleri, SPSS 16.0 programı ile yapıldı. Verilerin normal dağılıma uygunluğu Shapiro-Wilk testi ile değerlendirildi. Normal dağılım gösteren veriler parametrik testler kullanılarak analiz edildi.

Bulgular: Olguların ortalama vitamin B12 düzeyi 219±202 pg/ml olup, 169 vakada (%36.5) vitamin B12 eksikliği mevcuttu. Doğum ağırlıkları incelendiğinde vitamin B12 düzeyi düşük olan olgularda ortalama ağırlık 3298±482 gram iken vitamin B12 düzeyi normal olanlarda 3316±434 gram olarak bulundu (p=0.288). Doğum ağırlıkları doğum haftalarına göre düzenlenmiş persentillere ayrıldığında 39 olgunun (%9.8) 10 persentilin altında, 333 olgunun (%83.2) 10–90 persentil arasında, 28 olgunun (%7) ise 90 persentilin üzerinde olduğu saptandı. Bu sonuçlara göre iki grup arasında doğum ağırlıkları açısından anlamlı farklılık bulunmadı.

Sonuç: Çalışmamızın sonuçlarına göre vitamin B12 düzeyinin doğum ağırlığı ve doğum haftası üzerine istatistiksel olarak anlamlı bir etkisi saptanmamıştır.

Anahtar sözcükler: Gebelik, vitamin B12 eksikliği, doğum ağırlığı.

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Introduction

Vitamin B12 is a co-enzyme necessary for lipid, protein, carbohydrate and homocysteine metabolisms, erythropoiesis, and DNA and RNA synthesis.[1] Vitamin B12 has a significant role for cell division during pregnancy; it is synthesized in the liver and called as extrinsic factor. While it is effective in all cells, it is more active functionally in bone marrow, gastrointestinal system and central nervous system. It is a co-factor for the DNA synthesis in the bone marrow. In the deficiency of vitamin B12, depending on the insufficient DNA synthesis, erythroblasts cannot divide, they run into blood as megaloblasts and cause megaloblastic anemia.[1,2]

Vitamin B12 has a role in the reactions catalyzing the methionine synthesis from homocysteine. In this regard, B vitamins have a significant role in fetal growth, nutrition and development.[3–5] Anomalies that may occur in the metabolisms of methionine, homocysteine and cysteine cause poor obstetric outcomes such as placental dysfunction and preeclampsia.[6–8]

Although there are not much data about the physiological changes occurring in the vitamin B12 and vitamin B12 binding protein metabolism during pregnancy, it has been reported in some studies that biochemical vitamin B12 deficiency was observed in the third trimester at a rate of 35%.[9]

This study has been conducted to evaluate the changes that may be seen in the fetal birth weight in the deficiency of vitamin B12.

Methods

A total of 463 cases who referred for gestational follow-up between 28 and 32 weeks of gestation to the antenatal unit of gynecology and obstetrics clinic of a tertiary center between May 1, 2009 and September 21, 2009 were included in this study. The approval of local ethics board and written consent form of each patient were obtained for the study.

Age, pregnancy, delivery and abortion numbers, concurring chronic diseases, drug or smoking habits, and weeks of gestation according to their last menstrual period (LMP) of each case were investigated. Patients who were vegetarian, had a secondary disease that may cause vitamin B12 deficiency (thalassemia carrier, malabsorption syndromes, kidney diseases etc.) and history of delivering baby with neural tube defect were excluded from the study.

Vitamin B12 levels in serums obtained from fasting peripheral venous blood samples taken in the morning were analyzed by Beckman Coulter device (Beckman Coulter Inc., Pasadena, CA, USA) in the biochemistry laboratory. In order to determine vitamin B12 levels, the original kit of the device was used (Vitamin B12 access assay, Beckman Coulter Inc., Pasadena, CA, USA). Normal ranges of vitamin B12 levels were considered to be between 145 and 912 pg/ml.

Out of 463 cases included in the study, 400 patients delivered in our hospital. Of these 400 cases, delivery week and type, newborn body weight, 1-minute and 5-minute Apgar scores, and the presence of gestational complications observed during gestational follow-ups, preeclampsia, eclampsia, gestational diabetes mellitus (GDM), abruptio placentae, preterm labor, preterm premature rupture of membranes (PPROM), small for gestational age (SGA) and intrauterine growth retardation (IUGR) were recorded.

Classification of birth weights according to the gestational age was evaluated according to maturity and intrauterine growth curves defined by Hadlock (10). Accordingly, babies born with weights below 10th percentile according to gestational age were considered to be small for gestational age (SGA), those with weights between 10th and 90th percentile according to gestational age were considered to be appropriate for gestational age (AGA) and those with weights over 90th percentile were considered to be large for gestational age (LGA).[10]

Statistical Analysis

The statistical analyses of the data obtained from the study were performed by Statistical Package for Social Sciences version 16.0 (SPSS Inc., Chicago, IL, USA), the conformity of the data to normal distribution was evaluated by Shapiro Wilk test and the data showing normal distribution were analyzed by using parametric tests. The statistical analyses in the comparison between the groups were done by Student T test for mean values in data displaying continuity and by chi-square test in categorical variables. The relationship between vitamin B12 values and birth weight was analyzed by Pearson correlation test. The results were evaluated within 95% confidence interval. The value $p<0.05$ was considered statistically significant.

Results

Mean age of 463 cases included in the study was 26.1±5.1 (range: 17 to 40), the gravida was 1.92±1.10 (range: 1 to 7), number of deliveries was 1.26±0.70 (range: 0 to 6) and number of abortions was 1.31±0.67 (range: 1 to 4).

Mean vitamin B12 level of the cases was 219±202 pg/ml (range: 44 to 1516). Vitamin B12 level in 169 (36.5%) of the cases was lower than 145 pg/ml and they had vitamin B12 deficiency.

While 23 (5.0%) of the cases did not use any drug other than multivitamin including iron, 129 (27.9%) of them were using both multivitamin and antianemic preparation. The number of cases who were using only antianemic drug was 252 (54.4%). Fifty-nine (12.7%) cases were not using any preparation.

While B12 vitamin levels were normal in 129 (84.9%) of 152 cases using multivitamin, B12 vitamin levels were normal in 165 (53.1%) of 311 cases who were not using multivitamin. Vitamin B12 level was low in 46.9% of the cases not using multivitamin while it was low only in 15.1% of the cases using multivitamin. It was seen that vitamin B12 level of the cases using multivitamin was statistically and significantly higher (p<0.001) (**Table 1**).

Smoking habit during pregnancy was observed in 27 (5.8%) cases. While mean vitamin B12 level was 182±105 pg/ml in smoking cases, it was 221±205 pg/ml in non-smoking cases, and no significant difference was observed between the groups (p=0.331). Vitamin B12 levels were low in 14 (51.9%) smoking cases. Vitamin B12 levels were low in 155 (35.6%) of non-smoking cases. This difference was not statistically significant (p=0.088).

When vitamin B12 levels were analyzed according to the gravida, it was seen that 212 (45.8%) cases were primigravida. While mean vitamin B12 levels were 234±223 pg/ml in primigravida pregnant women, the levels were 206±181 pg/ml in multigravida pregnant women (p= 0.131). Vitamin B12 deficiency was found in 73 (34.4%) of primigravida pregnant women and in 96 (38.2%) of multigravida pregnant women (p=0.396).

In the study, 240 (51.8%) of the cases were nullipara and their mean vitamin B12 level was 228±212 pg/ml. For multipara pregnant women (parity ?1), the mean vitamin B12 level was found as 209±190 pg/ml (p=0.319). While vitamin B12 deficiency was observed in 84 (35%) of nullipara pregnant women, this rate was 38.1% (n=85) for multipara pregnant women. No difference was observed between the groups in terms of vitamin B12 deficiency (p=0.486).

When we reviewed the records of 400 cases who delivered in our hospital, we observed that mean week of gestation at delivery was 39 weeks and ? day ±1 week and 4 days (range: 32 weeks and 2 days – 42 weeks and 2 days), and birth weight was 3298±446 g (range:1470 to 4470 g). While 265 (66.2%) of the cases delivered vaginally, 135 (33.8%) of them delivered by cesarean section. After delivery, 1-minute Apgar score of all newborns was 7 and above.

In cases with low vitamin B12 levels (n=148), mean week of gestation at delivery was 39 weeks and 1 day ± 1 week and 3 days, and it was 39 weeks and 1 day±4 days in cases with normal vitamin B12 levels (p = 0.451). In terms of birth weights, mean weight was 3298±482 g in cases with low vitamin B12 levels while it was 3316±434 g in the cases with normal levels of vitamin B12 (p=0.288).

When birth weights were distributed into the percentiles according to the weeks of gestation, it was seen that 39 cases (9.8%) were below 10th percentile, 333 cases (83.2%) were between 10th and 90th percentile, and 28 cases (7%) were above 90th percentile. While the baby in 18 (12.2%) of a total 148 cases with low vitamin B12 level was small for gestational age, the babies were SGA in 21 (8.3%) of the cases with normal vitamin B12 levels. There was no significant impact of vitamin B12 deficiency on birth weight percentiles (p=0.321) (**Table 2**).

Table 1. Comparison of vitamin B12 levels in pregnant women who use and do not use multivitamin preparation.

Vitamin B12 level	Cases using multivitamin (n=152)	Cases not using multivitamin (n=311)	p value
Normal (n=294)	129 (%84.9)	165 (%53.1)	<0.01
Low (n=169)	23 (%15.1)	146 (%46.9)	

Table 2. Comparison of the groups according to vitamin B12 levels and birth weight percentiles..

Percentile	Vitamin B12 <145 pg/ml	Vitamin B12 ≥145 pg/ml	p value
<%10 (n=39)	18 (%12.2)	21 (%8.3)	
%10–90 (n=333)	122 (%82.4)	211 (%83.7)	0.321
>%90 (n=28)	8 (%5.4)	20 (%17.9)	

Also, statistically no significant correlation was found between birth weight vitamin B12 levels. (Pearson correlation test: r=0.080; p=0.108) (**Fig. 1**).

Gestational complications were diagnosed in 39 (8.4%) cases. Among them, preterm labor and PPROM were found in 16 (3.5%) cases, preeclampsia and IUGR in 13 (2.8%) cases, constitutional SGA in 3 (0.6%) cases, GDM in 5 (1.1%) cases, and disorder in liver function tests in 2 (0.4%) cases. While gestational complication developed in 17 (11.5%) of the cases with low vitamin B12 levels, it was developed in 22 (8.7%) of the cases with normal vitamin B12 levels (p=0.370). In terms of complication rates, there was statistically no significance between the two groups.

In the review of 361 cases who had no complication during pregnancy and delivered after 37 weeks of gestation, it was found that SGA developed in 12 (9.2%) of 131 cases with vitamin B12 deficiency and in 16 (7%) of 230 cases with normal B12 levels (p=0.378). Birth weight was 3353±407 g in cases with vitamin B12 deficiency and 3351±396 g in cases with normal vitamin B12 levels (p=0.847) (**Table 3**).

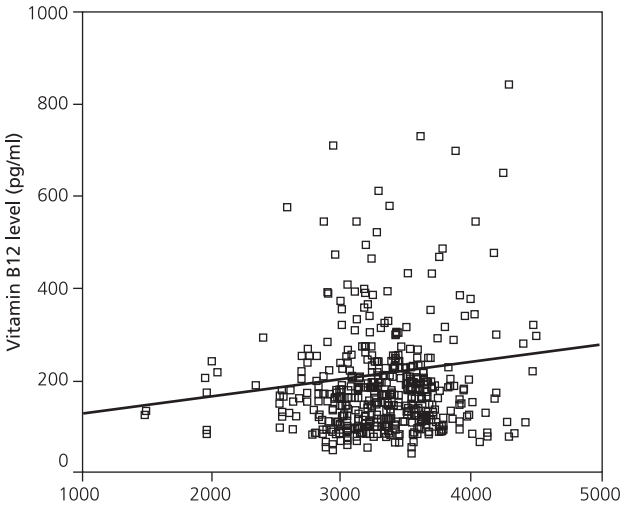

Fig. 1. Correlation between vitamin B12 level and birth weight (Pearson correlation test: r=0.080; p=0.108).

Discussion

In this study, we investigated to find the effects of vitamin B12 deficiency on fetal birth weight and obstetric outcomes. According to our findings, we observed no difference between the pregnant women groups with and without vitamin B12 deficiency in terms of birth weight and obstetric outcomes.

Vitamin B12 has a role in carbohydrate, lipid and protein metabolisms, DNA and RNA syntheses and in erythropoiesis. It is a co-factor necessary for cell division in pregnancy, and there are studies reporting that it is a significant element for fetal growth.[1,11] The value of this vitamin during pregnancy should be at a normal level for both fetal health and anemia control.

It was seen by our findings that vitamin B12 level of the cases using multivitamin was statistically and significantly higher (p<0.001). There are studies in the literature reporting that the use of multivitamin does not affect maternal serum vitamin B12 levels.[2] However, our findings correspond to the publications reporting opposite opinions.[12] Ray suggested that the use of multivitamin increases maternal vitamin B12 levels; however, it has no effect on birth weight.[12]

Although it is asserted that maternal vitamin B12 levels have a correlation with low birth weight and preterm labor, there are inconsistent data in the literature.[13,14] A relationship is claimed between erythrocyte folate concentrations at >16 weeks of gestation and infants with preterm and SGA.[15] It was determined that insufficient folate intake with diet and low folate levels at 28 weeks tripled preterm labor and low birth weight risks.[15] Although vitamin B12 deficiency is not associated with poor obstetric outcomes, a positive correlation was found between maternal vitamin B6 level and birth weight of infant.[15,16] In addition, an inverse correlation was found between cord blood vitamin B6 concentrations and preeclampsia which is a major risk factor for preterm labor.[15,17] Also, the role of homocysteine which may affect obstetric outcomes was investigated and a correlation was found between preeclampsia, low birth weight, preterm labor, and homocysteine which increases as a result of genetic anomalies or

Table 3. Vitamin B12 levels and mean birth weight and SGA prevalence in pregnancies terminated at term (n=361).

Vitamin B12 level	SGA	Birth weight (gram)
Low	12 (%9.2)	3353±407
Normal	16 (%7)	3351±396
p-value	0.378	0.847

folate, vitamin B12 or vitamin B6 levels at suboptimal levels.[18–22] In a recent study, it was suggested that maternal folate, vitamin B6 and vitamin B12 levels were not associated with low birth weight or SGA independently.[23] In another study, it was argued that folate and vitamin B12 supplement during pregnancy would provide improvements in parameters such as birth weight, head circumference and height.[24]

Although high homocysteine level was found to be associated with low birth weight, its correlation with vitamin B12 level could not be presented.[13,25] Also, it was found that vitamin B12 levels were not different in pregnancies with IUGR and normal delivery.[26] A study has been conducted to evaluated if maternal vitamin B12 level was an independent risk factor for increased IUGR frequency.[27] In this study, serum vitamin B12 level was found significantly in direct proportion with vitamin B12 intake; however, no relationship was detected between vitamin B12 intake and IUGR.[27] In women with low vitamin B6 and vitamin B12 levels and high homocysteine levels, a significant difference was found between DDA cases, SGA cases and the control group.[15] At the same time, preterm labor was found to be associated with vitamin B6 and B12 levels. It was found that the risk of preterm labor was 60% less in those with >258 pmol/L vitamin B12 levels than those with lower levels.[15]

Cross-sectional study setup and being unable to control all factors that may affect vitamin B12 levels metabolically are among the restrictions of our study. Also, we should not ignore the possibility of affecting findings with number of children, nutritional habits, and many socio-cultural, genetic and environmental parameters. In further studies, investigating parameters such as homocysteine, folate and vitamin B6 levels as well as vitamin B12 which are closely associated will help to interpret findings more healthily and reliably.

Conclusion

The results of our studies showed that maternal vitamin B12 deficiency had no effect on birth weight and delivery week. To clarify this matter, multi-centered, randomized and controlled studies to be conducted on wider series are required.

Conflicts of Interest: No conflicts declared.

References

1. Milman N, Byg KE, Bergholt T, Eriksen L, Hvas AM. Cobalamin status during normal pregnancy and postpartum: a longitudinal study comprising 406 Danish women. Eur J Haematol 2006;76:521–5.
2. Koebnick C, Hein UA, Dagnelie PC, Wickramasinghe SN, Ratnayaka ID, Hothorn T. Longitudinal concentrations of vitamin B12 and vitamin B12-binding protein during uncomplicated pregnancy. Clin Chem 2002;48:928–33.
3. Monsen AL, Schneede J, Ueland PM. Mid-trimester amniotic fluid methionine concentrations: a predictor of birth weight and length. Metabolism 2006;55;1186–91.
4. Dawson EB, Harris WA, Evans DR, Van Hook JW. Amniotic fluid amino and nucleic acid in normal and neural tube defect pregnancies. A comparison. J Reprod Med 1999; 44:28–32.
5. Rosenblatt DS, Whitehead VM. Cobalamin and folate deficiency: acquired and hereditary disorders in children. Semin Hematol 1999;36:19–34.
6. Aubard Y, Darodes N, Cantaloube M. Hyperhomocysteinemia and pregnancy-review of our present understanding and therapeutic implications. Eur J Obstet Gynecol Reprod Biol 2000; 93:157–65.
7. El-Khairy L, Vollset SE, Refsum H, Ueland P. Plasma total cysteine, mortality, and cardiovascular disease hospitalizations: the Hordaland Homocysteine Study. Clin Chem 2003; 49:895–900.
8. Nelen WL, Blom HJ, Steegers EA, den Heijer M, Eskes TK. Hyperhomocysteinemia and recurrent early pregnancy loss: a metaanalysis. Fertil Steril 2000;74:1196–9.
9. Allen LH. Vitamin B12 metabolism and status during pregnancy, lactation and infancy. Adv Exp Med Biol 1994;352: 173–86.
10. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: A sonographic weight standard. Radiology 1991; 181:129–33.
11. Chittaranjan S, Yajnik MD, Swapna SD, Anjali VP, Sadanand SN, Jyoti AD, et al. Maternal total homocysteine concentration and neonatal size in India. Asia Pac J Clin Nutr 2005;14: 179–81.
12. Ray JG, Blom HJ. Vitamin B12 insufficiency and the risk of fetal neural tube defects. QJM 2003;96:289–95.
13. Muthayya S, Dwarkanath P, Mhaskar M, Mhaskar R, Thomas A, Duggan CP, et al. The relationship of neonatal serum vitamin B12 status with birth weight. Asia Pac J Clin Nutr 2006;15:538–43.
14. Rao S, Yajnik CS, Kanade A, Fall CH, Margetts BM, Jackson AA, et al. Intake of micronutrient-rich foods in rural Indian mothers is associated with the size of their babies at birth. Pune Maternal Nutrition Study J Nutr 2001;131:1217–24.
15. Ronnenberg AG, Goldman MB, Chen D, Aitken IW, Willet WC, Selhub J, et al. Preconception homocystein and B vitamin status and birth outcomes in Chinese women. Am J Clin Nutr 2002;76:1385–91.

16. Reinken L, Dapunt O. Vitamin B6 nutriture during pregnancy. Int J Vitam Nutr Res 1978;48:341–7.
17. Ananth CV, Savitz DA, Luther ER, Bowes WA Jr. Preeclampsia and preterm birth subtypes in Nova Scotia, 1986 to 1992. Am J Perinatol 1997;14:17–23.
18. Rajkovic A, Catalano PM, Malinow MR. Elevated homocyst(e)ine levels with preeclampsia. Obstet Gynecol 1997;90: 168–71.
19. Rajkovic A, Mahomed K, Malinow MR, Sorenson TK, Woelk GB, Williams MA. Plasma homocyst(e)ine concentration in eclamptic and preeclamptic African women postpartum. Obstet Gynecol 1999;94:355–60.
20. Powers RW, Evans RW, Majors AK, Ojimba JI, Ness RB, Crombleholme WR, et al. Plasma homocysteine concentration is increased in preeclampsia and is associated with evidence of endothelial activation. Am J Obstet Gynecol 1998;179:1605–11.
21. Sorensen TK, Malinow MR, Williams MA, King IB, Luthy DA. Elevated second-trimester serum homocyst(e)ine levels and subsequent risk of preeclampsia. Gynecol Obstet Invest 1999;48:98–103.
22. Vollset SE, Refsum H, Irgens LM, Emblem BM, Tverdal A, Gjessing HK, et al. Plasma total homocysteine, pregnancy complications, and adverse pregnancy outcomes: the Hordaland Homocysteine Study. Am J Clin Nutr 2000;71: 962–8.
23. Chen LW, Lim AL, Colega M, Tint MT, Aris IM, Tan CS, et al. Maternal folate status, but not that of vitamins B-12 or B-6, is associated with gestational age and preterm birth risk in a multiethnic asian population. J Nutr 2015;145:113–20.
24. Gadgil M, Joshi K, Pandit A, Otiv S, Joshi R, Brenna JT, et al. Imbalance of folic acid and vitamin B12 is associated with birth outcome: an Indian pregnant women study. Eur J Clin Nutr 2014;68:726–9.
25. Yajnik CS, Deshpande SS, Panchanadikar AV, Naik SS, Deshpande JA, Coyaji KJ, et al. Maternal total homocysteine concentration and neonatal size in India. Asia Pac J Clin Nutr 2005;14:179–81.
26. Lindblad B, Zaman S, Malik A, Martin H, Ekström AM, Amu S, et al. Folate, vitamin b12 and homocysteine levels in South Asian women with growth-retarded fetuses. Acta Obstet Gynecol Scand 2005;84:1055–61.
27. Muthayya S, Kurpad AV, Duggan CP, Bosch RJ, Dwaranath P, Mhaskar A, et al. Low maternal vitamin B12 status is associated with intrauterin growth retardation in urban South Indians. Eur J Clin Nutr 2006;60:791–801.