International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Jahan N et al. Int J Reprod Contracept Obstet Gynecol. 2025 Feb;14(2):390-395
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20250171

Original Research Article

Vitamin B12 deficiency in pregnancy and its association with maternal and fetal outcomes

Noor Jahan[1]*, Kaniz Fatema[2], Tripti Rani Das[2], Hasna Hena Pervin[2], Riffat Ara Sharmin[3], Dipika Majumder[4], Fahmida Islam[5], Tabassum Tamanna[6], Meherun Nessa[7]

[1]Department of Obstetrics and Gynecology, Anmol Hospital and Research Centre, Kathmandu, Nepal
[2]Department of Obstetrics and Gynecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh
[3]Mirpur 10 Urban Dispensary, Civil Surgeon Office, Dhaka, Bangladesh
[4]250 Bed District Hospital, Madaripur, Bangladesh
[5]Department of Obstetrics and Gynecology, CIPRB, UNICEF
[6]Kushtia Medical College Hospital, Kushtia, Bangladesh
[7]NOVA IVF Fertility Clinic, Bangladesh

Received: 30 December 2024
Accepted: 27 January 2025

***Correspondence:**
Dr. Noor Jahan,
E-mail: jahandrnoor1984@gmail.com

ABSTRACT

Background: Pregnancy is a unique physiological state characterized by profound changes in a woman's body to support fetal growth and development. Adequate nutrition is vital during pregnancy to meet the increased demands of both the mother and the developing fetus. Among the various nutrients required during pregnancy, vitamin B12 stands out as a critical micronutrient. It plays a pivotal role in cellular replication, neurodevelopment, and the synthesis of DNA, making it essential for the proper growth and development of the fetus. This study was conducted to evaluate vitamin B12 deficiency in pregnancy and its association with maternal and fetal outcomes.

Methods: This was a cross-sectional study conducted among consecutively selected pregnant women who had just given birth to a single live baby admitted to the department of obstetrics and gynecology and also the department of feto-maternal medicine, Bangabandhu Sheikh Mujib medical university (BSMMU), Shahbagh, Dhaka from September 2022 to August 2023. A total of 90 women of 18-40 years of age at their 28-40 weeks of gestation were included in this study. Study subjects with vitamin B12 levels of <200 pg/ml were considered as the low level (group I), whereas level ≥200 pg/ml was considered as the normal (group II). Observations were undertaken on pregnancy complications and perinatal outcomes, which were compared between the two groups.

Results: The study revealed majority (57.8%) of the study participants age were within 26-34 years, a housewife was 74.4% and multigravida constituted 70.0% of the respondents. The 31 (34.4%) of the respondents had vitamin B12 level below 200 pg/mL and 59 (65.60%) women had normal serum vitamin B12 levels (≥200 pg/mL). Congenital hydrocephalus was observed in 16.1% of the group I mothers compared to only 1.7% in group II (p=0.017) and neural tube defect was present in 9.7% of group I but in none of group II mothers (p=0.038).

Conclusions: Mothers having vitamin B12 deficiency experience significantly higher rates of oligohydramnios, fetal hydrocephalus, and neural tube defects compared to those with normal vitamin B12 levels. However, there was no significant maternal complication.

Keywords: Vitamin B12, Feto-maternal outcome, Pregnant women

INTRODUCTION

Vitamins play a vital role in many biochemical functions in the human body and are essential components for maintaining optimal health. Vitamin B12, also known as cobalamin, is an important water-soluble vitamin that aids in the building of genetic material, production of normal red blood cells, and maintenance of the nervous system.[1] Vitamin B12, along with folic acid, is essential for fatty acid and amino acid metabolism, as well as DNA synthesis. It also plays a critical role in converting homocysteine to methionine, a process necessary for the production of neurotransmitters and phospholipids.[2] It is crucial for cellular growth, differentiation, and development.[3] Other than polymorphisms in vitamin B-12 metabolism-related genes; malabsorption and inadequate intake of animal-source foods are considered the principal causes of vitamin B12 deficiency.[4] Women are at a higher risk of deficiency during pregnancy due to the increased metabolic demands associated with physiological processes, including the growth of the placenta, fetus, and maternal tissues. As the pregnancy progresses, vitamin B12 deficiency becomes more prevalent, and the highest prevalence was reported during the third trimester.[5] Therefore, early recognition is important because low B12 levels in pregnancy have been associated with intrauterine growth restriction (IUGR), preeclampsia, preterm labor, low neonatal birth weight, neonatal neurological symptoms, and an increased rate of lower (uterine) segment cesarean section (LSCS).[6]

Vitamin B12 deficiency is one of the most frequent vitamin deficiencies worldwide. Vitamin B12 deficiency is marked by both hematological and neurological effects, ranging from mild symptoms such as fatigue and paresthesia to severe conditions like pancytopenia and spinal cord degeneration.[7] Diagnosis involves a serum cobalamin level below 148 pmol/L (200 ng/L) accompanied by clinical signs and symptoms and/or hematological indicators of deficiency. Alternatively, a serum cobalamin level below 148 pmol/L, along with elevated serum homocysteine or methylmalonic acid (MMA), is also diagnostic.[8] The overall prevalence of vitamin B12 deficiency in the United States is estimated to be around 6%. However, the condition is more common among specific populations, with higher rates observed in the elderly, pregnant women, and young children, ranging from 6% to 25%.[9] Despite supplementation, overall, 38% of Canadian pregnant women at delivery had vitamin B12 deficiency, while 43% were observed to have marginal levels at delivery.[10] India has the highest prevalence of Vitamin B12 deficiency, ranging from 47% to 71% in adults.[11] In Bangladesh, approximately 19% of women in early pregnancy experience vitamin B12 deficiency, while nearly 40% have marginal levels of deficiency.[5]

Structurally, vitamin B12 has two major parts: the corrin ring containing covalently bound cobalt, and a nucleotide base. Compounds with a corrin ring are called corrinoids, and those with the whole structure are cobalamin. The cobalamin active as coenzymes in humans is 5'-deoxy adenosylcobalamin and methylcobalamin. Others, including hydroxocobalamin and cyanocobalamin (the stable, commercial preparation), can also be converted to this enzymatically active cobalamin.[12] Its absorption requires binding to intrinsic factors, recognition of the complex by receptors in the terminal ileum, and release into the portal circulation bound to transcobalamin II or haptocorrin.[13] Transcobalamin II and haptocorrin play key roles in transporting cobalamin, with transcobalamin II delivering it to peripheral tissues and haptocorrin directing it to the liver. Consequently, significant amounts of vitamin B12 are stored primarily in the liver, as well as in the kidneys and other body tissues.[14]

During pregnancy, vitamin B12 supports normal folate metabolism, which is crucial for cell multiplication, particularly in the rapidly dividing tissues of the placenta and fetus. Additionally, research indicates that the placenta produces transcobalamin and contains receptors for it. Within the intervillous space of the placenta, vitamin B12, and folate are sequestered to ensure their distribution to the fetus. While the fetus utilizes the available vitamin B12 for essential biochemical reactions, it cannot synthesize the vitamin independently.[15]

During pregnancy, vitamin B12 supports normal folate metabolism, which is vital for cell multiplication, especially in the rapidly dividing tissues of the placenta and fetus. Studies have shown that the placenta produces transcobalamin and contains specific receptors for it. Within the intervillous space, vitamin B12 and folate are sequestered to facilitate their transfer to the fetus. The fetus relies on the available vitamin B12 for essential biochemical processes but cannot synthesize it independently.[2]

Vitamin B-12 deficiency and its impact on folate-mediated one-carbon metabolism result in metabolic impairments: homocysteine (Hcy) accumulation due to the failure to remethylate Hcy to methionine, impaired methionine, and S-adenosyl methionine biosynthesis, and the accumulation of 5-methyltetrahydrofolate, leading to impaired purine and thymidylate synthesis.[16] Therefore, higher levels of Hcy are related to increased oxidative stress and endothelial damage, which may increase the risk of developing preeclampsia.[17] Increased adiposity may also be associated with vitamin B12 deficiency, potentially contributing to insulin resistance and the development of gestational diabetes mellitus.[18] Moreover, an increased Hcy level was suggested to cause preterm labor through the induction of placental vascular endothelial dysfunction that persuades inflammatory, hormonal, or cellular (e.g., increased gap junctions) effects to instigate or hasten the sequence of events ending in preterm labor.[19] According to estimates, preterm birth constitutes about two-thirds of LBW babies, where the growth potential remains normal and appropriate for gestational age.[20] Furthermore, a sufficient supply of protein, energy, folic acid, and vitamin B12 plays a decisive role in erythropoiesis among

premature infants.[21] Experimental data suggest that a low cobalamin status in mothers has also been associated with a higher risk of neural tube defects, oral facial clefts, congenital heart disease, and spontaneous miscarriages.[22]

Bangladesh is the most densely populated country in the world. Despite significant economic progress and poverty reduction, around 10 percent of ever-married women reported being moderately or severely food insecure. Undernutrition is worsened by a lack of dietary diversity, as 70 percent of the diet is often made up of cereals, leading to insufficient intake of protein and essential micronutrients.[23] Therefore, considering the maternal nutritional deficiency status in Bangladesh, this study on maternal serum vitamin B12 status in pregnancy might clarify its potential relationship with the outcomes of pregnancy and the health of the mother and offspring.

METHODS

The study population was pregnant women of 18-40 years of age who had just given birth to a single live baby at 28-40 weeks of gestation admitted to the department of obstetrics and gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka. Maternal serum vitamin B12 assay was carried out on admission, and all the study subjects were observed till delivery. Based on the investigation reports, the study population was divided into two groups-group I: 31 patients with vitamin B12 deficiency i.e., <200 pg/ml (148 pmol/l). Group II: 59 patients with normal serum vitamin B12 concentration (≥200 pg/ml) consecutive sampling was done according to the availability of the patients who fulfilled the inclusion criteria.

Inclusion criteria

Women aged 18 to 40 years who will have given birth to single live babies after the age of viability (≥28 weeks), be admitted to the department of obstetrics and gynaecology, and department of fetomaternal medicine, BSMMU, Dhaka. Providing consent to participate in the study were included.

Exclusion criteria

Multiple gestations (e.g., twins, triplets), stillbirth or IUD, patients diagnosed with chronic medical conditions, e.g., pernicious anemia, chronic hypertension, overt diabetes mellitus, chronic renal disease, cardiovascular disease, chronic liver disease, thyroid disease, celiac disease, and vitiligo. Patients with chronic gastritis or a history of gastric bypass surgery, patients tested positive for HIV, hepatitis B, or syphilis infections, patients who have taken multivitamin supplementation within the last 4 months were excluded.

Statistical analyses were carried out by using the windows-based statistical package for social sciences (SPSS-27).

RESULTS

The cross-sectional study was carried out to evaluate whether there is any association between vitamin B12 deficiency and maternal and fetal outcomes. This study was carried out in department of obstetrics and gynaecology of BSMMU, Shahbag Dhaka. A total of 90 women who had just given birth were included in this study fulfilling the inclusion criteria. In each respondent, a vitamin B12 assay was performed, and they categorized as group I and II based on their vitamin B12 status.

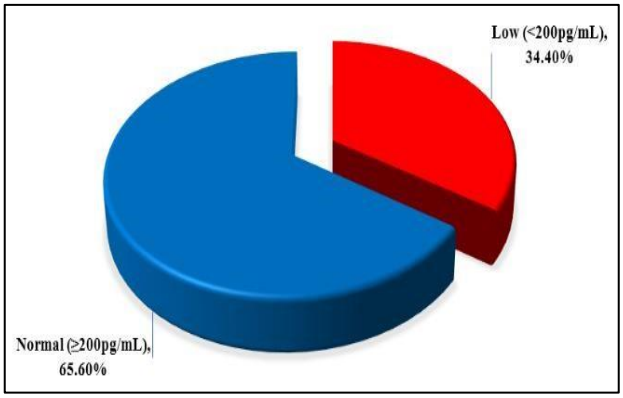

Figure 1: Distribution of vitamin B12 status among the study subjects.

Table 1: Distribution of the respondents according to demographic characteristics by group (Group I=31 and II=59).

Gravida	Group I, (n=31)	Group II, (n=59)	P value
Primigravida	6 (19.4)	21 (35.6)	0.110
Multigravida	25 (80.6)	38 (64.4)	

The above table shows that multigravida constituted 80.6% of group I and 64.4% of group II respondents. None of the differences in distribution was found statistically significant (p>0.05).

Table 2: Distribution of respondents according to personal history by group (Group I=31 and II=59).

Parameters	Group I, (n=31)	Group II, (n=59)	P value
History of PPI use for ≥12 months			
Yes	9 (29.0)	8 (13.6)	0.075
No	22 (71.0)	51 (86.4)	
Smoking			
Smoker	1 (3.2)	0 (0.0)	0.344
Nonsmoker	30 (96.8)	59 (100)	

Table 2 demonstrates that 29.0% of respondents in group I had a history of using PPI for an extended period (≥12 months), whereas only 13.6% of mothers in group II had a similar history of prolonged PPI use (p=0.075). In group I, only 1 out of 31 respondents (3.2%) reported being a

smoker, whereas none of respondents in group II were smokers (p>0.05).

Table 3: Distribution of the respondents according to BMI by group (Group I=31 and group II=59).

BMI (kg/m^2)	Group I, (n=31)	Group II, (n=59)	P value
Normal (18.5-24.9)	26 (83.9)	42 (71.2)	0.336
Overweight (25.0-29.9)	5 (16.1)	14 (23.7)	
Obese (>30)	0 (0.0)	3 (5.1)	

Table 3 denotes that 83.9% of the group I respondents had normal BMI compared to 71.2% of the group II mothers with normal vitamin B12 levels. This difference in the distribution of the respondents according to their BMI was statistically not significant (p>0.05).

Table 4: Distribution of the respondents according to maternal complication by group (Group I=31 and II=59).

Maternal complication	Group I, (n=31)	Group II, (n=59)	P value
Preeclampsia			
Yes	0 (0.0)	2 (3.4)	0.548[c]
No	31(100.0)	57 (96.6)	
PROM			
Yes	7 (22.6)	6 (10.2)	0.126[c]
No	24 (77.4)	53 (89.8)	
Puerperal sepsis			
Yes	1 (3.2)	0 (0.0)	0.344[c]
No	30 (96.8)	59 (100.0)	

Table 4 shows statistically no significant differences in the distribution of the respondents according to maternal complication of preeclampsia, PPROM, and puerperal sepsis between the two groups (p>0.05).

Table 5: Prevalence of fetal complications (Group I=31 and group II=59).

Complications	Group I, (n=31)	Group II, (n=59)	P value
Congenital hydrocephalus	5 (16.1%)	1 (1.7%)	0.017
Neural tube defect	3 (9.7%)	0 (0.0%)	0.038

The 16.1% of group I respondents had oligohydramnios in comparison to only 3.4% of group II mothers, which was found statistically significant (p=0.045).

DISCUSSION

The hospital-based cross-sectional analytical study was conducted to evaluate whether there is any association between vitamin B12 deficiency and maternal and fetal outcomes. This study was carried out in the department of obstetrics and gynaecology of BSMMU, Shahbag, Dhaka. A total of 90 women who had just given birth were included in this study fulfilling the inclusion criteria. In each respondent, a vitamin B12 assay was performed and they were categorized as group I and II based on their vitamin B12 status and then they were divided into two groups. Group I comprise patients with vitamin B12 deficiency i.e., <200 pg/ml (148 pmol/l), and group II comprises patients with normal serum vitamin B12 concentration (≥200 pg/ml).

It was observed that the majority (57.8%) belonged to the 26-34 years age group, over three-quarters (76.7%) were urban dwellers, 37.8% of the patient's level of education was higher secondary and above, 74.4% were housewives with 72.2% of the participants monthly family income within 10,000-20,000 Tk. More than two-thirds (70.0%) of participants were multigravida, while only 30.0% of women were primigravida. A nonsignificant difference was observed between the mean age of the respondents and their vitamin B12 levels. A similar study supports associations adjusted for potential sociodemographic confounders.[24] The 31 (34.4%) of the respondents had vitamin B12 levels were below 200 pg/mL and 59 (65.60%) women had normal serum vitamin B12 levels (≥200 pg/mL). A study revealed vit-B12 level was lower than 300 pg/mL in 93% of women. There was a statistically significant relationship between serum vitamin-B12 levels of pregnant women which did not support the finding of the present study and these dissimilarities might be due to small sample size and geographical variation.[25]

The present study informed that 29.0% of respondents in group I had a history of using PPI for an extended period (≥12 months), whereas only 13.6% of mothers in group II had a similar history of prolonged PPI use (p=0.075). In group I, only 1 out of 31 respondents (3.2%) reported being a smoker, whereas none of the respondents in group II were smokers (p>0.05). Another study revealed a non-significant difference between the prevalence of vitamin B12 deficiency (serum level <150 pm) and long-term PPI use which was similar in both groups which supports the findings of the present study.[26]

In the present study 83.9% of the group, I respondents had normal BMI compared to 71.2% of the group II mothers with normal vitamin B12 levels. This difference in the distribution of the respondents according to their BMI was statistically not significant. A similar study revealed Vit B12 deficiency may cause obesity.[18]

In the present study statistically, no significant differences were observed in the distribution of the respondents according to maternal complication of preeclampsia, PPROM, and puerperal sepsis between the two groups (p>0.05). Deshmukh reported that lower maternal vitamin B12 levels or an imbalance between vitamin B12 and

folate status are associated with a higher risk of pregnancy complications, such as recurrent pregnancy losses, gestational diabetes, pre-eclampsia, and other adverse outcomes which supports the finding of the present study.[24]

In group I (16.1%) and in group II (1.7%) had congenital hydrocephalus (p=0.017). Neural tube defect was found present in 9.7% of the group I respondents, which was absent in all group II patients (p=0.038). Insufficient levels of folate or vitamin B12 during pregnancy are associated with a higher risk of neural tube defects, impaired cognitive function, spontaneous abortion, stillbirth, fetal growth restriction, preterm delivery, and low birth weight which supports the findings of the present study.[27]

Limitations

There are some facts to be considered which might affect results-The study was conducted with a small sample size. So, it may not be adequate to represent the whole population. The present study was conducted over a very short period due to time constrain. Vitamin B12 deficiency is often accompanied by folate deficiency which could not be investigated in this study.

CONCLUSION

This study has shown that mothers with vitamin B12 deficiency experience significantly higher rates of fetal hydrocephalus, and neural tube defects compared to those with normal vitamin B12 levels. Given the severity of fetomaternal complications associated with vitamin B12 deficiency, there is an urgent need for public health initiatives to raise awareness, promote vitamin B12-rich diets, and implement appropriate supplementation strategies.

Recommendation

Further multicentred studies with larger sample sizes for longer periods may be carried out. Integrate routine screening for vitamin B12 deficiency into antenatal care to enable timely interventions and mitigate the risk of maternal and fatal complications. Healthcare providers should provide pregnant women with nutritional education and advice about the importance of a balanced diet with foods rich in vitamin B12.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Lykstad J, Sharma P. Vitamin B12. In: StatPearls. StatPearls Publishing. 2019. Available at: https://www.ncbi.nlm.nih.gov/books/NBK537204/. Accessed on 09 November 2024.
2. Barney AM, Abraham VJ, Danda S, Cherian AG, Vanitha S. Prevalence of Vitamin B12 deficiency and its associated risk factors among pregnant women of rural South India: a community-based cross-sectional study. Indian J Community Med. 2020;45(4):399.
3. Yajnik CS, Deshmukh US. Fetal programming: maternal nutrition and role of one-carbon metabolism. Rev Endocrine Metabolic Disord. 2012;13:121-7.
4. Allen LH. Causes of vitamin B12 and folate deficiency. Food Nutrit Bull. 2008;29(2):S20-34.
5. Sobowale OI, Khan MR, Roy AK, Raqib R, Ahmed F. Prevalence and Risk Factors of Vitamin B12 Deficiency among Pregnant Women in Rural Bangladesh. Nutrients. 2022;14(10):1993.
6. Kumawat DU, Amolsing D, Thakur DR. To study the status of vitamin b12 deficiency in pregnancy and its impact on the maternal and fetal outcome. Int J Clin Obstetr Gynaecol. 2021;5(3):243-55.
7. Dali-Youcef N, Andrès E. An update on cobalamin deficiency in adults. QJM. 2009;102(1):17-28.
8. Devalia V, Hamilton MS, Molloy AM, British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Brit J Hematol. 2014;166(4):496-513.
9. Allen LH. Bioavailability of vitamin B12. Int J Vitamin Nutr Res. 2010;80(4):330.
10. Visentin CE, Masih SP, Plumptre L, Schroder TH, Sohn KJ, Ly A, et al. Low serum vitamin B-12 concentrations are prevalent in a cohort of pregnant Canadian women. J Nutrit. 2016;146(5):1035-42.
11. Christian AM, Krishnaveni GV, Kehoe SH, Veena SR, Khanum R, Marley-Zagar E, et al. Contribution of food sources to the vitamin B12 status of South Indian children from a birth cohort recruited in the city of Mysore. Public Heal Nutrit. 2015;18(4):596-609.
12. Kräutler B. Biological organometallic chemistry of vitamin B12-derivatives. Advances in Bioorganometallic Chemistry Elsevier. 2019;399-430.
13. Pacifici GM. Effects of vitamin B12 in neonates and young infants. Int J Pediatr. 2016;4(6):1867-76.
14. Shipton MJ, Thachil J. Vitamin B12 deficiency-A 21st century perspective. Clin Med. 2015;15(2):145.
15. Molloy AM, Kirke PN, Troendle JF, Burke H, Sutton M, Brody LC, et al. Maternal vitamin B12 status and risk of neural tube defects in a population with high neural tube defect prevalence and no folic acid fortification. Pediatrics. 2009;123(3):917-23.
16. Finkelstein JL, Layden AJ, Stover PJ. Vitamin B-12 and perinatal health. Advances in Nutrition. 2015;6(5):55263.
17. Mardali F, Fatahi S, Alinaghizadeh M, Kord Varkaneh H, Sohouli MH, Shidfar F, et al. Association between abnormal maternal serum levels of vitamin B12 and preeclampsia: a systematic review and meta-analysis. Nutrition Rev. 2021;79(5):518-28.
18. Kanwal A, Bashir A. Vitamin B12 in Pregnancy and its relationship with Maternal BMI and Gestational

Diabetes Mellitus study from Pakistan. Pak J Med Sci. 2022;38(4Part-II):807.
19. Murad AW, Abdelhamid AA. Maternal serum homocysteine and uterine artery pulsatility index as predictors of spontaneous preterm labor. Evidence-Based Women's Health J. 2018;8(2):178-84.
20. WHO. Global Health Observatory (GHO) data. Mean Body Mass Index (BMI), 2019;50(3):117-28.
21. Haiden N, Klebermass K, Cardona F, Schwindt J, Berger A, Kohlhauser-Vollmuth C, et al. A randomized, controlled trial of the effects of adding vitamin B12 and folate to erythropoietin for the treatment of anemia of prematurity. Pediatrics. 2006;118(1):180-8.
22. Boxmeer JC, Macklon NS, Lindemans J, Beckers NG, Eijkemans MJ, Laven JS, Steegers EA, Steegers-Theunissen RP. IVF outcomes are associated with biomarkers of the homocysteine pathway in monofollicular fluid. Human Reproduct. 2009;24(5):1059-66.
23. USAID. Bangladesh: Food Security Country Framework (2017-2021). Available at: https://www.usaid.gov/sites/default/files/documents/1868/Bangladesh%2020Food%20Security%20Country%20Framework%20%2820172021%29.pdf. Accessed on 28 March 2024.
24. Behere RV, Deshmukh AS, Otiv S, Gupte MD, Yajnik CS. Maternal vitamin B12 status during pregnancy and its association with outcomes of pregnancy and health of the offspring: a systematic review and implications for policy in India. Front Endocrinol. 2021;12:619176.
25. Yetim A, Aygün E, Yetim Ç, Ucar A, Karakaş Z, Gökçay G, Demirkol M, Ömer B, Gökçay G, Baş F, Erginöz E. Measurement of serum vitamin B12-related metabolites in newborns: implications for new cutoff values to detect B12 deficiency. J Maternal-Fetal Neonatal Med. 2021;34(8):1260-8.
26. Den Elzen WP, Groeneveld Y, De Ruijter W, Souverijn JH, Le Cessie S, Assendelft WJ, et al. Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals. Alimentary Pharmacol Therapeut. 2008;27(6):491-7.
27. Yuan X, Han X, Zhou W, Long W, Wang H, Yu B, et al. Association of folate and vitamin B12 imbalance with adverse pregnancy outcomes among 11,549 pregnant women: An observational cohort study. Front Nutrit. 2022;9:947118.

Cite this article as: Jahan N, Fatema K, Das TR, Pervin HH, Sharmin RA, Majumder D, et al. Vitamin B12 deficiency in pregnancy and its association with maternal and fetal outcomes. Int J Reprod Contracept Obstet Gynecol 2025;14:390-5.