

Maternal Micronutrient Deficiency, Endocrine Dysregulation, and Adverse Pregnancy Outcomes: A Prospective Study on the Hidden Burden of Subclinical Malnutrition in Reproductive-Age Women

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Abstract

Background: Maternal micronutrient deficiencies can be asymptomatic but still lead to pregnancy complications and/or endocrine dysfunction. This study explored the understated burden of subclinical malnutrition and the nutritional–endocrine links to pregnancy.

Methods: A prospective observational cohort study was performed with 421 women with pregnancy. All socio-demographic, dietary, anthropometric, and obstetric parameters were collected. Hemoglobin, ferritin, vitamin D, vitamin B₁₂, folate, thyroid-stimulating hormone, free T4, fasting glucose, and HbA1c were measured. Follow-up was conducted until delivery. Independent t-test, Mann–Whitney U test, chi-square test/Fisher exact test, correlation analysis, and multivariable logistic regression were used to evaluate the associations.

Results: At least one micronutrient deficiency was identified in 286 (67.9%) participants, while 154 (36.6%) had two or more deficiencies. The most common were vitamin D deficiency (47.7%) and iron deficiency (44.7%). 101 (24.0%) women had endocrine/metabolic dysregulation. Overall, 176 (41.8%) experienced an adverse pregnancy outcome. The effects of vitamin D deficiency, iron deficiency, multiple micronutrient deficiencies, thyroid dysfunction, and abnormal glycemic regulation were all independent predictors of adverse outcomes. Those with both micronutrient deficiency and endocrine dysfunction had almost four times the adjusted odds of adverse outcomes.

Conclusions: Maternal malnutrition was subclinical, frequent, and linked to endocrine dysfunction and poor pregnancy outcomes. Better identification of high-risk pregnancies using Integrated nutritional and endocrine assessment.

Keywords: Pregnancy; Micronutrients; Malnutrition; Vitamin D; Iron deficiency; Thyroid dysfunction

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Introduction

Maternal nutrition is a major contributor to reproductive, obstetric, and fetal health, but often micronutrient deficiency is subacute and only becomes evident when pregnancy complications arise.[1] Subclinical malnutrition is a condition that can occur in women with a normal BMI, who may lack clinical stigmata of a nutrient deficiency, but whose iron, folate, vitamin B₁₂, vitamin D, iodine, or other micronutrient stores are not adequate to support the metabolic requirements of pregnancy.[2] Anaemia is one of the most common nutritional problems among women of reproductive age in the world.[3] Despite the improvements in maternal health care services, the World Health Organization (WHO) estimates that

30.7% of women aged 15-49 and 35.5% of pregnant women were nutrition vulnerable in 2023.[4] WHO also estimates that over 40% of all pregnant women in the world are anaemic and that at least half of this anaemic burden is related to iron deficiency.[5] In low- and middle-income countries, poor diet diversity, food insecurity, multiple pregnancies, lack of antenatal supplementation, and infection are coexistent and are especially significant.[6] In a specific situation, Pakistan is a highly vulnerable context. Previously, the national-level nutrition survey of 22,278 women of reproductive age revealed significant nutritional deficiencies, including 50.4% of them with anaemia, 50.8% with folate deficiency, and

52.4% with vitamin B12 deficiency.[7] Nutritional deficits may arise before conception and may reduce the physiological capacity of women to meet the growing demands for haemopoiesis, placental development, fetal growth, and maternal metabolic adaptations during pregnancy.[8]

Importantly, micronutrients are not solely used individually but are involved in multiple pathways within the endocrine system and metabolism.[9] Thyroid hormones are synthesized, metabolized, and regulated by iodine, iron, and selenium, and there is an increased need for iodine during pregnancy due to increased production, transfer to the fetus, and renal losses.[10] It has been shown that even mild iodine deficiency causes changes in maternal thyroid function, indicating that nutritional status can cause an endocrine disturbance before clinical thyroid disease occurs.[11] Likewise, vitamin D is no longer just known for its role in bone metabolism and health, but also its metabolic and endocrine regulatory activity.[12] Low maternal vitamin D status has been associated with compromised insulin sensitivity and glucose regulation, which might be a risk factor for gestational diabetes mellitus (GDM).[13]

In spite of the above-mentioned evidence, maternal micronutrient deficiencies and endocrine abnormalities are routinely evaluated as distinct clinical issues. A fragmented approach can underestimate the actual burden as women with several mild deficiencies may have no apparent symptoms, and may be considered nutritionally adequate based on anthropometry and/or periodic haemoglobin measurements. A prospective assessment starting early in pregnancy can thus be used to detect biochemical abnormalities before complications set in and to assess the risk of biochemical abnormality to come together with individual deficiency.

In this context, the present multicenter prospective study aimed to explore the unknown burden of subclinical malnutrition in reproductive-age women and its association with maternal endocrine dysfunction and pregnancy outcomes. The study will include the simultaneous assessment of micronutrient status and selected endocrine/metabolic markers as well as clinically important maternal and fetal outcomes, thereby transcending the framework of a single nutritional deficiency and investigating a nutritional–endocrine pathway. This study sought to identify the prevalence and distribution of micronutrient deficiencies in women of reproductive age, to determine if these deficiencies are associated with disorders of the endocrine system, and to assess if these deficiencies are independently or collectively associated with adverse pregnancy outcomes in reproductive-age women.

Methods

A prospective observational cohort study was carried out at DHQ Hospital Mianwali from 1st June, 2025 to 31st May, 2026 in the antenatal and obstetric departments. The recruitment of participants was done in the early months of the study, and all women recruited were followed prospectively from baseline assessment until delivery.

A sample size was determined using OpenEpi version 3.01 for the estimation of a single population proportion. Sample size estimation was done assuming the expected prevalence of vitamin D deficiency as an example of a well-documented micronutrient deficiency in a pregnant population. In a previous study in Pakistan, antenatal women were found to have 43 out of 90 (47.77%) vitamin D deficient.[14] Based on the estimated prevalence of 47.77%, a 95% confidence level, and an absolute precision of 5%, the minimum sample size was estimated to be 382 individuals to be recruited. The sample was inflated to 421 participants because of the 10% possibly lost to follow-up, incomplete lab measures, and withdrawals prior to delivery. Thus, 421 pregnant women were targeted for recruitment.

A non-probability consecutive sampling technique was used. Women between 18 and 45 years of age with a confirmed intrauterine pregnancy who attended antenatal care were included in the study. Women aged between 18 and 45 years with a confirmed intrauterine pregnancy who attended antenatal care during the recruitment period. Women had to be willing to give informed consent, undergo a pretest biochemical evaluation, and be available for follow-up until delivery. Multiple gestation pregnancies were included to reduce the confounding effect of multiple gestation on maternal nutritional requirements and pregnancy outcomes. Patients with any pre-existing endocrine disease were excluded.

Other exclusions were women who had chronic renal or hepatic disease, known malabsorptive disease, active malignancy, or severe systemic illness or known hematological disease that is not due to nutritional deficiency. When supplementation was expected to significantly modify the baseline biochemistry, women who were receiving therapeutic doses of vitamin D, vitamin B12, folate, iron, iodine before enrolment were excluded. Multiple pregnancies, pregnancies complicated by known major congenital anomalies at enrolment, and pregnancies for which follow-up was not desired were also excluded.

Written informed consent was obtained prior to a structured baseline assessment. Data regarding the sociodemographic factors were obtained. In addition, detailed information on diet, food diversity, and prenatal supplement use, history of any pregnancy complications, interpregnancy interval, smoking

exposure, and medical history was collected. At the initial antenatal assessment, blood samples were taken for baseline purposes. Maternal nutritional status was evaluated using complete blood count (CBC) and serum biochemical tests. Additionally, the micronutrient panel consisted of serum ferritin, vitamin B₁₂, folate, and 25-OH-vitamin D, and other biochemical parameters were measured as per the study laboratory protocol. Biochemical thyroid dysfunction was evaluated through TSH and free thyroxine levels, and maternal glycemic state was evaluated through fasting glucose and/or HbA_{1c} levels. Fasting insulin was measured to investigate metabolic dysregulation.

Micronutrient deficiency was characterized based on predetermined laboratory limits or internationally recognized clinical definitions. The serum levels of 25-hydroxyvitamin D, ferritin, vitamin B₁₂, and folate were classified as deficient, insufficient, or adequate, when applicable. Laboratory reference ranges and pregnancy-specific diagnostic criteria for thyroid and glucose abnormalities were used for the definitions of endocrine deregulation. Blood samples were taken under uniform standardization conditions and processed in a uniform or harmonized laboratory method at all centers to avoid analytical variation.

Participants were afterwards followed up using antenatal records and programmatic follow-up assessments. Relevant pregnancy complications were recorded, such as gestational diabetes mellitus, gestational hypertension, pre-eclampsia, anemia, threatened and/or spontaneous pregnancy loss, preterm delivery, premature rupture of membranes, and other clinically relevant maternal complications. Gestational age, mode of delivery, birth weight, Apgar scores, small-for-gestational age, neonatal admission, and other neonatal outcomes were recorded at delivery. Any of the prespecified adverse maternal or fetal/neonatal outcomes was considered the primary pregnancy outcome, and secondary outcomes, in each case, were analyzed individually.

IBM SPSS Statistics 27.0 was used to enter, clean, and analyze the data. All continuous variables were evaluated for normality via the Shapiro-Wilk test and with graphing. Continuous variables were expressed as mean $\pm$ standard deviation, and skewed variables as median (IQR). Categorical variables were displayed as frequencies and percentages. Micronutrient and endocrine baseline parameters were compared between women with and without adverse pregnancy outcomes. The independent-samples t-test and Mann-Whitney U test were used for comparison of continuous variables according to data distribution, while the chi-square test and Fisher's exact test were used for categorical variables. Pearson correlation coefficient was used to assess the correlation between

micronutrient concentrations and endocrine/metabolic parameters.

A binary logistic regression model was used to assess the relationship between each micronutrient deficiency, each endocrine disorder, and the composite adverse pregnancy outcome. Variables showing clinical relevance and $p < 0.20$ in the univariable analysis were included in the multivariable analysis. The final model was adjusted for potential confounders, such as maternal age, BMI, parity, socioeconomic status, education, dietary intake, prenatal supplementation, and relevant obstetric characteristics. Odds ratios (aORs) with 95% confidence intervals (CIs) were reported. A separate analysis was conducted to assess the relationship between multiple micronutrient deficiencies and endocrine dysregulation and increasing risk of adverse pregnancy outcomes. A two-sided p -value < 0.05 was regarded as significant.

Results

A total of 421 pregnant women were included in the study, with 176 of those women (41.8%) having an adverse pregnancy outcome. The mean maternal age was 28.9 ± 5.4 years and mean BMI was 24.8 ± 3.6 kg/m². The factors affecting adverse outcomes in women were significantly different, with women with adverse outcomes being significantly older and more likely to have low socioeconomic status, inadequate dietary diversity, previous pregnancy loss, and no regular prenatal supplementation compared to women with favorable outcomes, while BMI, place of residence, employment status, and gravidity were not significantly different (Table 1).

The majority of the micronutrient abnormalities were vitamin D (47.7%) and iron deficiency (44.7%), followed by vitamin B₁₂ deficiency (33.7%) and folate (27.6%). In total, 67.9% suffered from at least one micronutrient deficiency and 36.6% suffered from two or more micronutrient deficiencies. Of these, 15.2% had thyroid dysfunction and 13.8% had abnormal glycemic regulation. Women with adverse outcomes had significantly lower levels of hemoglobin, ferritin, vitamin D, and vitamin B₁₂, and a significantly higher prevalence of individual and multiple micronutrient deficiencies, thyroid dysfunction, and abnormal glycemic regulation than those without adverse outcomes (Table 2).

Significant correlations were observed between selected micronutrient and metabolic parameters. Vitamin D was weakly inversely correlated with TSH, fasting glucose, and HbA_{1c}; vitamin B₁₂ was weakly inversely correlated with TSH and fasting glucose, and weakly directly correlated with free T₄. The majority of correlations between ferritin and folate were not statistically significant (Table 3).

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Women who were micronutrient deficient and had endocrine/metabolic dysregulation were more likely to experience adverse maternal and neonatal outcomes. Women with nutrition or endocrine abnormalities had significantly higher rates of gestational diabetes, preeclampsia, preterm delivery, low birth weight, small-for-gestational-age, low Apgar score, and admission to the NICU, and there was a relative increase in caesarean delivery rate (Table 4).

Iron-deficiency, vitamin-D deficiency, vitamin-B12 deficiency, multiple micronutrient deficiencies, thyroid dysfunction, and abnormal glycemic regulation were still independently associated with adverse pregnancy outcomes after adjusting for relevant sociodemographic, anthropometric, dietary, and obstetric variables. Two or more micronutrient deficiencies were the most strongly associated nutritional contribution, and any endocrine/metabolic dysregulation was associated with >2-fold greater odds of an adverse outcome (Table 5).

When nutrition and endocrine abnormalities were combined, a combined-risk pattern was observed. Wisconsin women with micronutrient deficiency alone had 1.78 times higher adjusted odds of adverse pregnancy outcomes than women with no abnormality; women with endocrine dysregulation alone had 2.13 times higher adjusted odds of adverse pregnancy outcomes than women with no abnormality; and women with both abnormalities had 3.92 times higher adjusted odds of adverse pregnancy outcomes than women with no abnormality ($p<0.001$). Therefore, the group with subclinical micronutrient deficiency and an insulin problem was the highest-risk group identified (Table 6).

Table 1. Sociodemographic, anthropometric, dietary and obstetric characteristics according to pregnancy outcome

Variable	No adverse outcome (n=245) n(%)/mean ± SD	Adverse outcome (n=176) n(%)/mean ± SD	p-value
Age, years	28.3 ± 5.2	29.8 ± 5.5	0.006
Age ≥30 years	81 (33.1)	76 (43.2)	0.039
BMI, kg/m ²	24.5 ± 3.4	25.2 ± 3.8	0.061
BMI ≥25 kg/m ²	91 (37.1)	77 (43.8)	0.179

Urban residence	150 (61.2)	99 (56.3)	0.321
Secondary education or higher	177 (72.2)	109 (61.9)	0.027
Low socioeconomic status	85 (34.7)	86 (48.9)	0.004
Employed	57 (23.3)	37 (21.0)	0.573
Primigravida	108 (44.1)	66 (37.5)	0.184
Previous pregnancy loss	33 (13.5)	39 (22.2)	0.027
Previous preterm birth	18 (7.3)	20 (11.4)	0.171
Interpregnancy interval <2 years*	48 (19.6)	43 (24.4)	0.255
Inadequate dietary diversity	88 (35.9)	95 (54.0)	<0.001
Regular prenatal supplement use	174 (71.0)	100 (56.8)	0.002
Passive smoking exposure	40 (16.3)	43 (24.4)	0.045
*Among previously pregnant women.			

Table 2. Baseline micronutrient and endocrine/metabolic status according to pregnancy outcome

Variable	No adverse outcome (n=245)	Adverse outcome (n=176) n(%)/mean ± SD	p-value
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	n(%)/ mean ± SD		
Hemoglobin, g/dL	11.0 ± 1.2	10.5 ± 1.4	<0.001
Anaemia	99 (40.4)	106 (60.2)	<0.001
Ferritin, ng/mL	21.1 (12.8–32.5)	15.0 (8.6–25.3)	<0.001
Iron deficiency	91 (37.1)	97 (55.1)	<0.001
25-OH vitamin D, ng/mL	21.4 ± 7.9	17.1 ± 6.9	<0.001
Vitamin D deficiency	96 (39.2)	105 (59.7)	<0.001
Vitamin B12, pg/mL	262.4 ± 94.1	227.5 ± 84.8	<0.001
Vitamin B12 deficiency	65 (26.5)	77 (43.8)	<0.001
Folate, ng/mL, median (IQR)	6.3 (4.4–8.7)	5.4 (3.8–7.4)	0.002
Folate deficiency	53 (21.6)	63 (35.8)	0.001
≥1 micronutrient deficiency	144 (58.8)	142 (80.7)	<0.001
≥2 micronutrient deficiencies	67 (27.3)	87 (49.4)	<0.001
TSH, mIU/L, median (IQR)	2.28 (1.54–3.21)	2.61 (1.72–3.79)	0.018
Free T4, ng/dL	1.05 ± 0.18	1.00 ± 0.20	0.012
Thyroid dysfunction	27 (11.0)	37 (21.0)	0.007

Fasting glucose, mg/dL	90.1 ± 9.6	93.9 ± 11.9	<0.001
HbA1c, %	5.2 ± 0.4	5.4 ± 0.6	<0.001
Abnormal glycemic regulation	24 (9.8)	34 (19.3)	0.007
Any endocrine/metabolic dysregulation	45 (18.4)	56 (31.8)	0.002

Table 3. Correlations between micronutrient concentrations and endocrine/metabolic parameters

Micronutrient	TSH	Free T4	Fasting glucose	HbA1c
25-OH vitamin D	−0.12 (0.014)	0.10 (0.041)	−0.21 (<0.001)	−0.18 (<0.001)
Ferritin	−0.08 (0.104)	0.07 (0.151)	−0.09 (0.071)	−0.06 (0.218)
Vitamin B12	−0.10 (0.039)	0.12 (0.014)	−0.11 (0.026)	−0.09 (0.067)
Folate	−0.06 (0.219)	0.08 (0.102)	−0.07 (0.147)	−0.05 (0.289)

Values are Pearson correlation coefficients (r), with p-values in parentheses.

Table 4. Pregnancy and neonatal outcomes according to baseline micronutrient/endocrine status

Outcome	≥1 micronutrient	No deficiency	Endocrine	No endocrine
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	deficiency n (%)	n (%)	dysregulation n (%)	dysregulation n (%)
Gestational diabetes mellitus	48 (16.8)	10 (7.4)	27 (26.7)	31 (9.7)
Gestational hypertension	31 (10.8)	8 (5.9)	16 (15.8)	23 (7.2)
Pre-eclampsia	27 (9.4)	4 (3.0)	15 (14.9)	16 (5.0)
Preterm delivery <37 weeks	40 (14.0)	8 (5.9)	18 (17.8)	30 (9.4)
PROM	34 (11.9)	8 (5.9)	14 (13.9)	28 (8.8)
Spontaneous pregnancy loss	13 (4.5)	2 (1.5)	5 (5.0)	10 (3.1)
Low birth weight <2500 g	54 (18.9)	9 (6.7)	22 (21.8)	41 (12.8)
Small for gestational age	43 (15.0)	8 (5.9)	18 (17.8)	33 (10.3)

Maternal age				
Apgar score <7 at 5 min	15 (5.2)	3 (2.2)	7 (6.9)	11 (3.4)
NICU admission	34 (11.9)	5 (3.7)	15 (14.9)	24 (7.5)
Caesarean delivery	112 (39.2)	45 (33.3)	45 (44.6)	112 (35.0)

Table 5. Multivariable logistic regression analysis of predictors of adverse pregnancy outcomes

Predictor	Adjusted OR	95% CI	p-value
Age ≥30 years	1.48	1.01–2.18	0.044
BMI ≥25 kg/m ²	1.22	0.82–1.82	0.326
Low socioeconomic status	1.67	1.11–2.51	0.014
Inadequate dietary diversity	1.89	1.27–2.82	0.001
No regular prenatal supplementation	1.61	1.08–2.40	0.019
Iron deficiency	1.74	1.15–2.63	0.008
Vitamin D deficiency	2.08	1.39–3.12	<0.001
Vitamin B12 deficiency	1.52	1.00–2.31	0.049
Folate deficiency	1.36	0.87–2.12	0.178
≥2 micronutrient deficiencies	2.41	1.56–3.73	<0.001

Thyroid dysfunction	1.91	1.13–3.23	0.016
Abnormal glycemic regulation	1.83	1.05–3.19	0.033
Any endocrine/metabolic dysregulation	2.14	1.38–3.32	0.001

Table 6. Combined association of micronutrient deficiency and endocrine dysregulation with adverse pregnancy outcomes

Risk category	Adverse outcome (%)	Adjusted OR	95% CI	p-value
No deficiency + normal endocrine profile	25 (26.0)	1.00	Reference	—
≥1 micronutrient deficiency only	91 (40.6)	1.78	1.04–3.05	0.036
Endocrine dysregulation only	18 (46.2)	2.13	1.05–4.33	0.036
Micronutrient deficiency + endocrine dysregulation	42 (67.7)	3.92	2.05–7.50	<0.001

Discussion

The current prospective study showed that there was a significant degree of subclinical maternal malnutrition and endocrine/metabolic dysregulation. Almost one-

third of the participants were deficient in one or more micronutrients, and over one-third were deficient in two or more micronutrients. Vitamin D deficiency was the most common abnormality, followed by iron, vitamin B12, and folate deficiency. Micronutrient abnormalities were not only biochemical; they were also linked to adverse maternal and neonatal outcomes, and were independently associated with adverse pregnancy outcomes, even after accounting for important sociodemographic, anthropometric, dietary, and obstetric factors. The prevalence of micronutrient deficiency in women with endocrine/metabolic dysregulation was also significant, as women with both disorders had nearly four times the adjusted odds of an adverse pregnancy outcome. The results were consistent with this idea that subclinical malnutrition could be a nutritional–endocrine disorder in itself, rather than being a group of separate deficiencies.

The prevalence of micronutrient deficiency found in the present research was similar to other studies reporting the high prevalence of micronutrient deficiency, especially in low- and middle-income countries, which found that deficiencies occur with greater frequency during pregnancy. A 2021 systematic review and meta-analysis of maternal iron status and the health of children included 44 studies and over 127,849 mother–child pairs.[15] There was substantial heterogeneity reported, but about half of the studies included suggested a link between low maternal iron status or iron deficiency and adverse childhood outcomes. The authors pointed out that the maternal iron status may impact outcomes beyond just maternal anaemia. The data from this study also indicated that 44.7% of women were iron deficient and that iron deficiency was independently associated with poor pregnancy outcomes, further substantiating the clinical significance of screening for iron depletion prior to more severe iron deficiency symptoms.[15] It was noteworthy that vitamin D deficiency was common in our cohort. Multivariably, vitamin D deficiency was associated with adverse pregnancy outcomes, as was found in the univariate analyses. This result aligns with the systematic review and dose-response meta-analysis of maternal vitamin D status and adverse pregnancy outcomes conducted by Zhao et al. in 2022, which indicated a relationship between low maternal vitamin D status and a range of adverse outcomes.[16] More recently, Chien et al. conducted an umbrella review in 2024 which included 16 systematic reviews and meta-analyses with 250,569 women. The risks of recurrent miscarriage, preterm birth, small-for-gestational-age, or low birth weight were associated with vitamin D deficiency.[17] These results were similar to our observation that vitamin D-deficient women had an increased incidence of GDM,

preterm delivery, low birth weight and SGA. A consistent association between low vitamin D levels and poor adaptation to pregnancy was observed across the various study designs, which further supported the plausibility of an association between vitamin D and pregnancy adaptation.

A recent prospective pregnancy cohort from 2025 also confirmed our findings, specifically looking at maternal vitamin D status and fetal growth patterns throughout pregnancy. That study followed up vitamin D status during the first and second trimesters of pregnancy with respect to fetal growth and pregnancy outcomes, a critical question of when to assess vitamin D status.[18] In particular, the prospective design of that investigation, and the prospective follow-up in our study, minimized the chance that it was a biochemical side effect of a already established pregnancy complication that was being studied. However, some variation in the population studied, vitamin D thresholds, sampling time, and supplementation habits may account for some variability in the size of the associations between studies.

In our study, vitamin D was associated with abnormal glycemic regulation, adding another layer to the nutritional–endocrine link. There was a weak but statistically significant inverse association between vitamin D and fasting glucose ($p<0.001$) and HbA1c ($p<0.001$), and abnormal glycemic regulation was more prevalent in women with adverse pregnancy outcomes. This finding was in line with the findings of an umbrella review in 2024 that showed that vitamin D deficiency was associated with GDM.[17] The study was supported by a recent meta-analysis of 68 studies that reported significantly lower serum vitamin D levels in women with GDM.[19] The relationships that we observed here were relatively small in magnitude and occurred in the absence of any causal links, but there was evidence that there might be a relationship between micronutrient status and metabolic adaptation to pregnancy.

In our analysis, vitamin B12 deficiency showed a moderate association with adverse pregnancy outcomes, with a higher prevalence found in women than in multiple micronutrient deficiency, and was identified as an independent predictor of adverse pregnancy outcomes. This finding was biologically plausible since vitamin B12 is involved in DNA synthesis, erythropoiesis, methylation reactions, and neurological development in the fetus. The findings have not been as consistent, however, for B12 and pregnancy outcomes as they have been with vitamin D. In 2023, the Cochrane review of vitamin B12 supplementation included 5 trials with 984 women who were pregnant, and concluded that supplementation had beneficial effects on maternal B12 levels and biochemical deficiency, but the

evidence was inconclusive for preterm birth and low birth weight.[20] Therefore, our observation of an association between B12 deficiency and adverse outcomes must be viewed as indication of a potential risk marker and not as evidence of a direct causal relationship between B12 deficiency and adverse outcomes.

Multiple micronutrient deficiencies seemed to have greater clinical significance than single deficiencies. In this study, among women with at least two deficiencies, their adjusted odds of an adverse pregnancy outcome were more than twice as high. This was in line with findings that support a more holistic maternal nutrition approach. Multiple micronutrient supplementation was linked to fewer low-birth-weight infants, fewer SGA births, and fewer preterm births when compared to iron-folic acid supplementation in a recent systematic review of the literature conducted in 2021 for low- and middle-income countries. Likewise, a 2023 study of multiple-micronutrient supplementation during pregnancy found that multiple-micronutrient supplementation reduced the risk of low birth weight and SGA, and that in studies that relied on ultrasound to assess gestational age, multiple-micronutrient supplementation had a beneficial effect on preterm birth.[21] These results corroborated our hypothesis that individual nutrient deficiencies could underestimate the synergistic biological impact of multiple deficiencies.

Another important observation of the present study was finding the association between nutritional deficiency and endocrine dysfunction. Thyroid dysfunction was present in 15.2% of participants and was independently associated with adverse pregnancy outcomes. The same finding was observed in a 2022 individual-participant-data meta-analysis of maternal thyroid function and gestational hypertension and pre-eclampsia conducted by Toloza et al. There were clinically significant relationships between thyroid abnormalities and hypertensive pregnancy complications.[22] Our findings also confirmed those of Han et al., 2023, who conducted a systematic review and meta-analysis focusing on isolated hypothyroxinemia and adverse outcomes of pregnancy and the neonatal period.[23] These results were consistent and indicated that even mild thyroid changes might be a clue to women who are at risk during pregnancy.

This was further confirmed by the latest evidence. In 2026, Zhang et al. published an umbrella review that included 25 systematic reviews and meta-analyses on 58 maternal outcomes and 90 offspring outcomes. Gestational diabetes, pre-eclampsia, miscarriage, premature rupture of membranes, postpartum haemorrhage, anaemia, preterm birth, altered birth weight, and low Apgar scores were all associated with

maternal thyroid dysfunction. The negative outcomes we observed in our cohort, however, were very similar to the outcomes seen in the current literature, especially GDM, hypertensive disorders, preterm delivery, low birth weight, SGA, and low Apgar scores.[24]

The clinical relevance of the finding that abnormalities of glycemic regulation occurred independently and were related to adverse pregnancy outcomes was also important. Among women in our cohort, 13.8% had abnormalities of glycemic regulation, and these women had significantly higher rates of adverse outcomes. This relationship was observed in parallel with a relationship between vitamin D deficiency and glucose measures, suggesting that there was a biological link between nutritional and endocrine abnormalities. In the context of pregnancy, vitamin D status, metabolic regulation, inflammation, and thyroid function may interact, but are not independent pathways. Given the present results, the findings are therefore preliminary support for a larger model that suggests that insufficient micronutrient reserves may affect maternal metabolic adaptation and lead to greater vulnerability to pregnancy complications.

These findings, overall, indicated that maternal subclinical malnutrition occurred at a relatively high prevalence and was clinically significant, especially when associated with multiple micronutrient deficiencies and endocrine/metabolic dysregulation. The findings were largely consistent with current evidence that hypovitaminosis D, iron deficiency, multiple micronutrient deficiency, thyroid dysfunction, and metabolic abnormalities are associated with poor pregnancy outcomes. The special aspect of the present study was the integrated assessment of these factors in a prospective multicenter design. The results suggested that maternal malnutrition and endocrine dysfunction are not unique conditions, but also a nutritional-endocrine risk phenotype during pregnancy. Identification of this phenotype early in pregnancy may offer a window for nutritional and metabolic intervention to prevent adverse maternal and fetal outcomes.

Limitations

There were a number of limitations in the study. First, it was difficult to make causal inferences between micronutrient deficiency, endocrine dysfunction, and poor pregnancy outcomes with its observational study design. Secondly, the multi-center design enhanced the representativeness of women who were treated in tertiary-care hospitals, but it may not have included women who access care in primary or rural health care. Third, the concentrations of the micronutrients might have been affected by gestational age, dietary levels, inflammation, supplements, and illness. Fourth, relatively few endocrine and micronutrient

abnormalities were present, decreasing the statistical power of the subgroup analyses. Lastly, unmeasured dietary, genetic, environmental, and socioeconomic factors that might cause residual confounding were not fully ruled out.

Conclusion

Subclinical maternal micronutrient deficiency was very common, and these deficiencies were related to endocrine/metabolic dysfunction and adverse pregnancy outcomes. Vitamin D and iron deficiency were especially prevalent, and having multiple micronutrient deficiencies and endocrine abnormalities together had significantly higher odds of adverse outcomes. The results indicated that the conventional assessment, which is mainly symptom-based or haemoglobin concentration-based, might underestimate the maternal nutritional risk. Early detection of nutritional and endocrine abnormalities, especially for women who lack dietary diversity or supplementation, could offer a chance for targeted antenatal intervention. Future interventional studies are justified to explore the effects of correcting combined nutritional and endocrine abnormalities on maternal and neonatal outcomes.

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