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Prepregnancy obesity is an independent risk factor for neonatal vitamin K deficiency at birth

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ABSTRACT

Background: Neonatal vitamin K deficiency (VKD) is a known risk factor for vitamin K deficiency bleeding (VKDB), a potentially life-threatening condition. However, maternal risk factors for VKD at birth remain poorly understood.
Objective: This study aimed to identify maternal factors associated with neonatal VKD at birth, with a focus on prepregnancy obesity.
Methods: We conducted a retrospective matched case–control study of neonates admitted to our hospital between 2018 and 2023. VKD was defined as serum protein induced by vitamin K absence-II (PIVKA-II) levels ≥1000 mAU/mL on day 0 of life before vitamin K administration. For each VKD case, two gestational age- and sex-matched controls were selected. Maternal background characteristics were compared, and multivariate logistic regression was performed to identify independent risk factors for neonatal VKD.
Results: Among 64 neonates with VKD and 128 controls, maternal prepregnancy obesity (body mass index ≥25) was significantly more common in the VKD group. Multivariate analysis identified prepregnancy obesity as an independent risk factor for neonatal VKD (odds ratio 3.97, $P < 0.001$). Additionally, maternal prepregnancy BMI was positively correlated with neonatal PIVKA-II levels at birth ($r = 0.285$, $P < 0.0001$).
Conclusions: Maternal prepregnancy obesity is independently associated with an increased risk of VKD in neonates at birth. These findings suggest that targeted evaluation and vitamin K management strategies are warranted in pregnancies complicated by maternal obesity.

Introduction

Neonates are often born with vitamin K deficiency (VKD), which is especially evident in preterm and low birth weight infants, making them more susceptible to vitamin K deficiency bleeding (VKDB) than otherwise healthy infants [1]. Neonatal VKDB is categorized into early, classic, and late types based on the timing of onset [2]. All forms of VKDB can be severe for neonates, highlighting the need for accurate assessment of neonatal VKD to ensure appropriate prevention measures. PIVKA-II, a protein induced by vitamin K absence, is commonly used as a marker for VKD. Since PIVKA-II levels increase with the severity of deficiency, it allows for the detection of VKD and related coagulation disorders before they become clinically significant [3]. In our facility, we routinely measure PIVKA-II levels at birth to screen for VKD [4]. It is well established that VKDB can be prevented by promptly administering vitamin K preparations in cases of VKD [5]. Furthermore, a recent study by Perrone et al. demonstrated that oral supplementation of phylloquinone (VK1) after discharge significantly reduced PIVKA-II levels in exclusively breastfed term infants [6]. Identifying the risk of VKD before delivery would enable the implementation of more effective VKDB prevention strategies. Therefore, understanding maternal factors during pregnancy that contribute to neonatal VKD risk is crucial for preventing VKDB.

Several case reports have documented the occurrence of VKDB during the fetal period in infants born to mothers with malnutrition-related conditions, such as hyperemesis gravidarum [7], eating disorders [8], and Crohn's disease [9]. Additionally, neonatal VKDB in the early postnatal period has been reported in infants born to mothers who used vitamin K antagonists, including anticoagulants (coumarin and warfarin), antiepileptic drugs

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(carbamazepine, phenytoin, and barbiturates), or antituberculosis agents (rifampin and isoniazid) [10,11]. In contrast, studies on neonatal VKD observed immediately after birth and its maternal risk factors are limited. The only available report is of a small-scale case-control study from China that investigated the prevalence and risk factors of vitamin K_2 deficiency in neonates and identified antenatal steroid administration as an independent risk factor [12]. Interestingly, in adults, obesity is known to increase the risk of fat-soluble vitamin deficiencies, and it has been suggested that adipose tissue may influence the plasma concentrations, metabolism, and organ-specific actions of fat-soluble vitamins [13].

Furthermore, studies have reported that vitamin K concentrations in adipose tissue are higher than those observed in other organs, indicating a negative correlation between body fat percentage and vitamin K levels. Additionally, PIVKA-II levels were significantly higher in individuals with a higher body fat percentage than in those with a lower body fat percentage [14]. However, it remains unclear whether maternal prepregnancy obesity is a risk factor for neonatal VKD in the early postnatal period.

Therefore, this study aimed to identify maternal risk factors for neonatal VKD using a matched case-control study. Furthermore, we sought to elucidate the impact of maternal prepregnancy obesity on elevated PIVKA-II levels immediately after birth.

Methods

We included neonates admitted to our hospital between June 1, 2018, and September 30, 2023, for whom PIVKA-II levels were measured at birth. Maternal information was extracted from electronic medical records, including age at pregnancy, gestational age (weeks), parity, delivery mode, presence of premature rupture of membranes (PROM), use of antenatal steroids, use of antibiotics, presence of placental abnormalities, prepregnancy weight (kg), prepregnancy BMI (kg/m^2), weight gain during pregnancy, presence of underlying conditions (endocrine diseases, psychiatric or neurological disorders, collagen-related diseases, hypertensive disorders of pregnancy, gestational diabetes, malnutrition, and gastrointestinal diseases), history of medication use during pregnancy (anticoagulants and antiepileptic drugs), and laboratory data analyzed within 2 weeks of delivery. Neonatal information, including gestational age, sex, birth weight, and small for gestational age (SGA), was also extracted. Day 0 PIVKA-II level (before vitamin K administration) $\geq$1000 mAU/mL was defined as VKD. Based on previously published criteria, a serum PIVKA-II level >1000 mAU/mL represents an unequivocally abnormal accumulation of undercarboxylated prothrombin and has been used in laboratory studies as a marker of experimental VKD [4,15]. The exclusion criteria were multiple pregnancies, neonatal cases transferred from other facilities without maternal medical records, and cases lacking maternal weight information.

A matched case-control study was conducted using electronic medical records. For each VKD case, two non-VKD cases were selected as controls, forming the VKD and control groups, respectively. Specifically, for each case in the VKD group, two non-VKD neonates admitted during the same period with the same gestational age and sex and whose birthdates were closest to those of the patient with VKD were selected as controls. To prevent duplication, once a control case was selected, it was removed from the pool for subsequent selections. First, maternal background factors were compared between the two groups to identify factors contributing to the occurrence of neonatal VKD. Next, multivariate analysis was performed to determine independent risk factors associated with neonatal VKD occurring shortly after birth. In the multivariate analysis, logistic regression was conducted using maternal background factors that showed significant differences between the two groups in the univariate analysis, as well as factors identified in previous studies as risk factors for maternal vitamin deficiency (e.g., maternal age at pregnancy and history of previous deliveries) as independent variables. The presence or absence of neonatal VKD (defined as a PIVKA-II level $\geq$1000 mAU/mL on day 0) was used as the dependent variable. Finally, a correlation analysis was performed to investigate the relationship between the maternal background factors identified in the multivariate analysis and neonatal PIVKA-II levels at birth (prior to vitamin K administration).

Blood samples were obtained directly from the neonates immediately after birth (not from the umbilical cord) and promptly centrifuged. PIVKA-II levels were measured using a two-step sandwich CLEIA with the LumipulsePresto PIVKAII-N kit (SEKISUI MEDICAL Inc., Japan), as previously described [4]. The data are expressed in arbitrary units, with 1 AU corresponding to 1 μg of purified prothrombin. The vitamin K prophylaxis method in our hospital involves administering vitamin K_2 (menatetrenone) intravenously, if available, or orally within 24 hours of birth (1 mg for infants with birthweight <1500 g and 2 mg for infants with birthweight $\geq$1500 g). The second dose (2 mg) is administered intravenously or orally at 4 days of age in all cases [4]. Antenatal steroids, such as betamethasone 12 mg (up to two doses), were administered intramuscularly. Placental abnormalities were defined as the presence of any of the following findings: placenta previa, placental abruption, or pathological findings such as chorioamnionitis, funisitis, placental hemangiomatosis, or placental infarction. SGA was defined as a birth weight below the 10th percentile for the corresponding gestational age [16]. Advanced maternal age was defined as 35 years or older. Prepregnancy obesity was defined as a BMI $\geq$ 25 kg/m^2. Cases in which intravenous fluid therapy was required during pregnancy due to hyperemesis gravidarum or similar conditions were classified as having nutritional deficiency during pregnancy.

Data are presented as median [range], mean ± SD, or number (%), as applicable. The Mann–Whitney nonparametric rank test, chi-square test, and Fisher's exact test were used to compare data between the two groups, as appropriate. Logistic regression analysis was used for multivariate analysis. Correlations between two variables were assessed using Spearman's rank correlation coefficient. Statistical significance was set at $P < 0.01$. Analyses were performed using GraphPad Prism 10 software (GraphPad Software, Inc., La Jolla, CA, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee at Kobe University Graduate School of Medicine (IRB approval number: B240085, August 7, 2024). All parents provided written informed consent for the use of their children's personal medical data.

Results

From June 1, 2018 to September 30, 2023, 2694 neonates were admitted to our institute. We excluded 235 neonates without PIVKA-II level measurements on day 0 (prior to vitamin K administration). Of the remaining patients, 96 neonates had PIVKA-II levels $\geq$1000 mAU/mL on day 0. After excluding twin pregnancies (6), patients without maternal medical records (6), and patients without maternal weight information (20), 64 patients were included in the VKD group (Fig. 1). For comparison, 128 neonates were chosen as the control group.

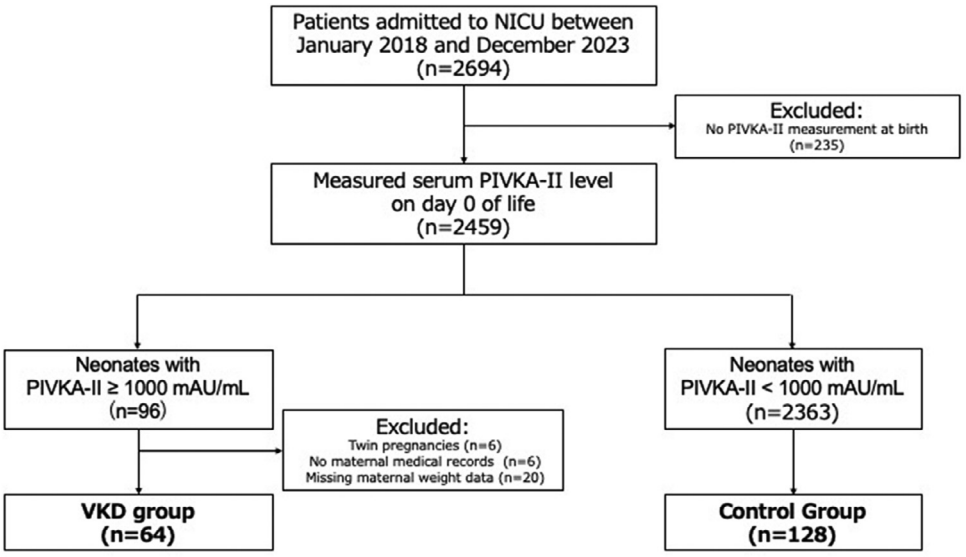

Fig. 1. Flowchart of patient selection.Of 2694 neonates admitted between January 2018 and December 2023, 2459 had serum PIVKA-II level measurements at birth. After applying the exclusion criteria, 64 neonates with PIVKA-II ≥1000 mAU/mL were extracted to form the VKD group. The control group comprised 128 neonates without VKD, matched for gestational age and sex. VKD, vitamin K deficiency; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

Comparison of maternal characteristics between the two groups

A comparison of maternal characteristics between the VKD and control group revealed no significant differences in maternal age (VKD group: 32 [20–47] years vs. control group: 33.5 [19–45] years), primiparity (41 cases [64%] vs. 82 cases [64%]), Cesarean section rate (32 cases [50%] vs. 50 cases [39%]), incidence of premature rupture of membranes (11 cases [17%] vs. 34 cases [27%]), use of antenatal steroids (2 cases [3%] vs. 3 cases [2%]), use of antibiotics (36 cases [56%] vs. 70 cases [55%]), presence of placental abnormalities (31 cases [74%] vs. 51 cases [71%]), weight gain during pregnancy (8.6 [−7.6–25] kg vs. 10.1 [−1.7–20.5] kg), or incidence of SGA (7 cases [11%] vs. 10 cases [8%]) (all $P > 0.01$). However, significant differences were observed in the prepregnancy weight (57.5 [42–115] kg vs. 51 [38–108] kg, $P < 0.01$) and BMI (20.5 [16.5–41.8] kg/m^2 vs. 19.3 [14.8–40.2] kg/m^2, $P < 0.01$) between the groups. Regarding maternal comorbidities, a significant difference was found in the proportion of mothers with malnutrition and gastrointestinal diseases (6 cases [9%] vs. 1 case [1%], $P < 0.01$). Regarding medication history, there were no significant differences in the proportions of mothers using anticoagulants or antiepileptic drugs (Table 1).

Similarly, no significant differences were found in blood test parameters between the two groups (Table 2).

Maternal factors contributing to neonatal VKD at birth

Logistic regression analysis was conducted to identify maternal background factors that contributed to neonatal VKD at birth (defined as PIVKA-II levels ≥1000 mAU/mL on day 0, prior to vitamin K administration). Independent variables included maternal background factors that showed significant differences in the univariate analysis (prepregnancy obesity [BMI ≥ 25 kg/m^2], presence of nutritional deficiencies during pregnancy, or a history of gastrointestinal diseases), as well as maternal factors previously identified as risk factors for vitamin deficiency in multiple studies (advanced maternal age and history of previous deliveries). Furthermore, maternal factors previously identified by Liu et al. as independent risk factors for VKD—specifically antenatal corticosteroid administration, delivery by cesarean section, and the presence of SGA—were also incorporated into the analysis [12]. Logistic regression analysis identified prepregnancy obesity ($P < 0.001$, odds ratio [OR] 3.97) as a maternal background factor that contributes to neonatal VKD at birth (Table 3).

Correlation between maternal prepregnancy BMI and neonatal PIVKA-II levels

A positive correlation was observed between maternal prepregnancy BMI and neonatal PIVKA-II levels on day 0 (before vitamin K

Table 1
Comparison of maternal characteristics between the VKD and control groups.

	VKD group (n = 64)	Control group (n = 128)	*P* value
Age at pregnancy (years)	32 (20–47)	33.5 (19–45)	0.99
Gestational age at birth (weeks)	39 (26–41)	39 (26–41)	1.00
Primiparity	41/64 (64%)	82/128 (64%)	1.00
Cesarean section rate	32/64 (50%)	50/128 (39%)	0.17
Premature rupture of membranes, PROM	11/64 (17%)	34/128 (27%)	0.21
Use of antenatal steroids	2/64 (3%)	3/128 (2%)	1.00
Use of antibiotics	36/64 (56%)	70/128 (55%)	0.88
Placental abnormalities	31/42 (74%)	51/72 (71%)	0.83
Small for gestational age, SGA	7/64 (11%)	10/128 (8%)	0.59
Prepregnancy weight (kg)	57.5 (42–115)	51 (38–108)	<0.01
Prepregnancy BMI (kg/m^2)	20.5 (16.5–41.8)	19.3 (14.8–40.2)	<0.01
BMI<18.5 (kg/m^2)	4/64 (6%)	19/128 (15%)	0.10
BMI≥18.5, BMI<25 (kg/m^2)	36/64 (56%)	90/128 (70%)	0.08
BMI≥25 (kg/m^2)	24/64 (38%)	19/128 (15%)	<0.01
Weight gain during pregnancy (kg)	8.6 (−7.6 to 25)	10.1 (−1.7 to 20.5)	0.08
Gestational diabetes	7/64 (11%)	17/128 (13%)	0.82
Hypertensive disorders of pregnancy	4/64 (6%)	12/128 (9%)	0.59
Endocrine disorders	15/64 (23%)	21/128 (16%)	0.25
Psychiatric or neurological disorders	10/64 (16%)	16/128 (13%)	0.66
Collagen-related diseases	12/64 (19%)	20/128 (16%)	0.68
Malnutrition and gastrointestinal diseases	6/64 (9%)	1/128 (1%)	<0.01
Use of anticoagulants	1/64 (2%)	0/128 (0%)	0.33
Use of antiepileptic drugs	1/64 (2%)	3/128 (2%)	1.00

VKD, vitamin K deficiency; PROM, premature rupture of membranes; SGA, small for gestational age; BMI, body mass index.

Table 2
Comparison of maternal laboratory data between the VKD and control groups

	VKD group (n = 64)	Control group (n = 128)	*P* value
CBC			
WBC count (/μL) (n = 62, n = 128)	8450 (4400–15500)	8100 (3300–27200)	0.35
Neutrophil (/μL) (n = 61, n = 123)	6621 (3126–13464)	6030 (1934–24208)	0.27
Eosinophil (/μL) (n = 61, n = 123)	58 (0–378)	62 (0–670)	0.27
Basophil (/μL) (n = 61, n = 123)	25 (0–90)	29 (0–193)	0.48
Monocyte (/μL) (n = 61, n = 123)	416 (213–806)	415 (102–1904)	0.97
Lymphocyte (/μL) (n = 61, n = 123)	1390 (272–2705)	1351 (655–2899)	0.51
Platelets ($\times 10^4$/μL) (n = 62, n = 128)	23 (10–38)	22 (10–44)	0.30
RBC count ($\times 10^6$/μL) (n = 62, n = 128)	3.87 (2.81–5.18)	3.83 (2.88–5.21)	0.84
Hemoglobin (g/dL) (n = 62, n = 128)	11.2 (7.3–14.0)	11.0 (8.1–15.2)	0.80
Hematocrit (%) (n = 62, n = 128)	33.8 (25.0–41.7)	33.5 (25.8–43.7)	0.95
MCV (fL) (n = 62,n = 128)	87.5 (73–102)	88.0 (67–104)	0.53
MCH (pg) (n = 62, n = 128)	28.8 (21.7–35.3)	29.3 (19.7–35.7)	0.49
MCHC (%) (n = 62, n = 128)	32.8 (24.4–35.4)	33.0 (26.1–35.1)	0.42
Reticulocytes (%) (n = 49, n = 95)	2.1 (1.4–7.1)	2.2 (1.4–4.1)	0.96
Coagulation status			
APTT (sec) (n = 62, n = 128)	28.3 (24.3–61.2)	28.1 (23.3–56.8)	0.60
PT-INR (n = 62, n = 128)	0.97 (0.86–1.16)	0.96 (0.81–1.10)	0.17
Fibrinogen (mg/dL) (n = 60, n = 126)	403 (170–702)	417 (151–636)	0.45
Antithrombin Ⅲ (%) (n = 61, n = 128)	84 (61–112)	85 (54–363)	0.41
D-Dimer (μg/mL) (n = 62, n = 128)	2.40 (0.8–24.4)	2.45 (0.6–10.0)	0.76
Biochemistry			
TP (g/dL) (n = 61, n = 125)	6 (5.3–7.2)	6 (3.5–6.9)	0.60
ALB (g/dL) (n = 61, n = 125)	3 (2.2–3.9)	3 (1.1–3.7)	0.40
CRP (mg/dL) (n = 62, n = 126)	0.27 (0.01–4.65)	0.16 (0.01–5.21)	0.11
AST (IU/L) (n = 62, n = 126)	17 (10–403)	17 (10–113)	0.33
ALT (IU/L) (n = 62, n = 128)	10 (4–755)	10 (4–110)	0.53
γ-GTP (U/L) (n = 62, n = 127)	10 (4–374)	9 (5–74)	0.85
ALP (U/L) (n = 60, n = 120)	157 (77–587)	155 (18–316)	0.88
LD (U/L) (n = 62, n = 126)	186 (125–434)	183 (113–575)	0.44
CK (U/L) (n = 62, n = 125)	46.5 (10–1627)	51.0 (11–231)	0.87
ChE (U/L) (n = 51, n = 106)	233.0 (129–383)	240.5 (95–503)	0.51
Na (mEq/L) (n = 62, n = 126)	137 (134–140)	137 (126–140)	0.27
K (mEq/L) (n = 62, n = 126)	3.9 (3.3–4.6)	4.0 (3.3–5.1)	0.20
Cl (mEq/L) (n = 62, n = 126)	107 (100–111)	107 (99–114)	0.93
Ca (mg/dL) (n = 59, n = 117)	8.6 (7.8–9.4)	8.5 (6.4–9.7)	0.66
P (mg/dL) (n = 51, n = 97)	3.6 (2.3–5.6)	3.4 (2.2–4.2)	0.05
BUN (mg/dL) (n = 62, n = 126)	7.75 (4.3–16.5)	8.7 (3.1–22.1)	0.05
Cre (mg/dL) (n = 62, n = 126)	0.51 (0.31–0.90)	0.52 (0.32–1.07)	0.29
eGFRcre (mL/min/1.73m$^{2)}$ (n = 62, n = 126)	109.35 (58.0–196.4)	108.7 (45.5–175.6)	0.39
UA (mg/dL) (n = 62, n = 126)	4.45 (2.3–8.2)	4.50 (1.9–8.9)	0.30
T-BIL (mg/dL) (n = 61, n = 122)	0.6 (0.3–1.1)	0.6 (0.3–1.0)	0.73
D-BIL (mg/dL) (n = 57, n = 117)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.07
T-Chol (mg/dL) (n = 51, n = 95)	267 (163–395)	276 (28–1030)	0.71
HDL (mg/dL) (n = 49, n = 94)	79 (40–128)	83 (36–146)	0.40
TG (mg/dL) (n = 49, n = 94)	308.0 (154–604)	257.5 (55–4639)	0.04

VKD, vitamin K deficiency; CBC, complete blood count; WBC, white blood cell; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; APTT, activated partial thromboplastin time; PT-INR, prothrombin time-international normalized ratio; TP, total protein; ALB, albumin; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; LD, lactate dehydrogenase; CK, creatine kinase; ChE, cholinesterase; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; P, phosphorus; BUN, blood urea nitrogen; Cre, creatinine; eGFRcre, estimated glomerular filtration rate based on creatinine; UA, uric acid; T-BIL, total bilirubin; D-BIL, direct bilirubin; T-Chol, total cholesterol; HDL, high-density lipoprotein; TG, triglycerides.

Table 3
Multivariate logistic regression analysis for risk factors associated with VKD

	Odds ratio	95% confidence interval (CI)	*P* value
Advanced maternal age	0.623	0.313–1.24	0.17
Multiparity	1.16	0.58–2.34	0.67
Prepregnancy obesity	3.97	1.90–8.34	<0.01
Malnutrition and gastrointestinal diseases	14.6	1.59–134.00	0.02
Use of antenatal steroids	0.992	0.302–3.26	0.99
Cesarean section rate	1.3	0.662–2.55	0.44
SGA	1.64	0.508–5.32	0.41

Prepregnancy obesity was defined as BMI ≥ 25 kg/m^2. Advanced maternal age was defined as maternal age ≥ 35 years. SGA was defined as birth weight below the 10th percentile for gestational age.
VKD, vitamin K deficiency; SGA, small for gestational age; BMI, body mass index; CI, confidence interval.

administration) (Spearman's rank correlation coefficient = 0.285, $P < 0.0001$) (Fig. 2).

Discussion

In this study, we found that maternal prepregnancy obesity independently predicted VKD development in neonates at birth. Additionally, maternal prepregnancy BMI showed a weak positive correlation with neonatal PIVKA-II levels on day 0 (prior to vitamin K administration).

To date, few large-scale studies have investigated the maternal risk factors associated with neonatal VKD at birth. To the best of our knowledge, the only study that has addressed the prevalence and risk factors for neonatal vitamin K_2 deficiency is a case–control study conducted in China [12]. In that study, vitamin K_2 levels were

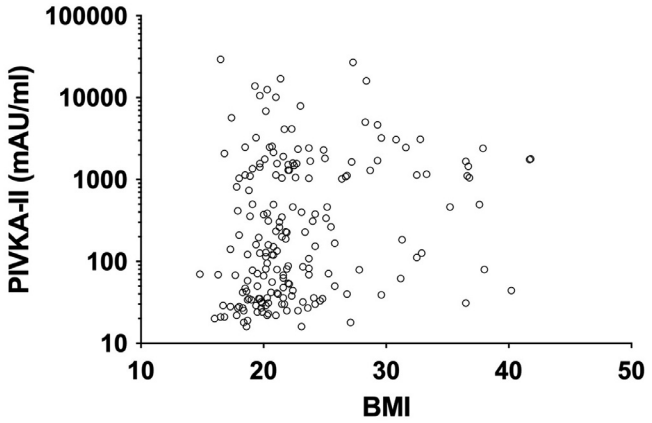

Fig. 2. Correlation between BMI and PIVKA−II levels. BMI correlates with PIVKA-II levels (mAU/mL, r = 0.285, $P < 0.0001$); PIVKA-II, protein induced by vitamin K absence or antagonist-II.

measured within 24−72 hours after birth in 200 neonates, and multivariate logistic regression analysis identified antenatal corticosteroid administration, cesarean delivery, and SGA status as significant independent risk factors for subclinical VKD. In contrast, our study did not find antenatal corticosteroid use, cesarean delivery, or SGA to be significant predictors of VKD at birth. Instead, we identified maternal prepregnancy obesity as an independent risk factor, suggesting a different risk profile from that previously reported. In our previous report analyzing 1759 newborns admitted between June 2018 and March 2022, the proportion of infants with serum PIVKA-II levels ≥1000 mAU/mL at birth was 3.7% (n = 65/1759), with a mean value of 216 ± 1072 mAU/mL [4]. This incidence provides important context for interpreting the maternal risk factors identified in the present study. In the study by Liu et al., serum vitamin K levels were used as the indicator of deficiency. However, circulating vitamin K concentrations do not necessarily reflect its bioavailability or utilization in target tissues. Furthermore, owing to the extremely low endogenous levels of vitamin K, its measurement is technically challenging [17]. In fact, Liu et al. reported that vitamin K_2 levels were below the limit of detection in 24 neonates. In contrast, our study used serum PIVKA-II levels as a marker of VKD, which offers a more practical and sensitive method that requires only a small sample volume. PIVKA-II was detectable in all neonates included in our study. Moreover, the Liu study lacked matching between the VKD and control groups in terms of baseline neonatal characteristics. Our study employed a matched case−control design, matching gestational age and sex between the groups, thereby minimizing bias and potential confounders during control selection. Additionally, Liu et al. evaluated a limited set of maternal background factors, whereas we included detailed maternal data, including prepregnancy weight and laboratory parameters, allowing for a more comprehensive analysis of potential risk factors.

To our knowledge, this is the first study to demonstrate that maternal prepregnancy obesity independently predicts VKD occurrence in neonates at birth. A nationwide Finnish study by Kuitunen et al. that analyzed the incidence of obesity and morbid obesity among pregnant women, as well as the effects of maternal obesity on delivery mode, perinatal and neonatal mortality, and neonatal outcomes, reported that neonates born to mothers with morbid obesity (BMI ≥ 40 kg/m^2) had increased rates of intensive care unit admissions (aOR 2.21; 95% CI: 2.10−2.32), higher perinatal mortality (aOR 1.65; 95% CI: 1.28−2.14), and higher neonatal mortality (aOR 1.68; 95% CI: 1.04−2.72) [18]. Additionally, a study by Bodnar et al. that evaluated the independent effects of prepregnancy BMI on maternal and neonatal 25-hydroxyvitamin D [25(OH)D] levels found that women with obesity (BMI ≥ 30 kg/m^2) had significantly lower adjusted mean serum 25(OH)D concentrations at 4−22 weeks of gestation compared to those without obesity (BMI < 25 kg/m^2) (56.5 vs. 62.7 nmol/L, $P < 0.05$), with a higher prevalence of vitamin D deficiency (61% vs. 36%, $P < 0.01$). Furthermore, neonates born to mothers with obesity had lower adjusted mean 25(OH)D levels at birth (50.1 vs. 56.3 nmol/L, $P < 0.05$) [19]. These findings underscore the known impact of maternal obesity on neonatal outcomes and vitamin status. However, to the best of our knowledge, no previous study has reported an association between maternal obesity and neonatal VKD.

It has been previously reported that fat-soluble vitamins are concentrated and stored in human adipose tissue [20−24]. In adult populations, obesity is associated with an increased risk of fat-soluble vitamin deficiency. It has been suggested that adipose tissue may influence the circulating concentrations, metabolism, and tissue-specific actions of fat-soluble vitamins [13]. For example, obesity-related vitamin D deficiency has been suggested to result from the sequestration of vitamin D in adipose tissue, thereby limiting its bioavailability [25]. Ravera et al. reported that vitamin K_2 levels were significantly lower in obese patients undergoing dialysis [24]. Similarly, Shea et al. found that individuals with higher body fat percentages had significantly elevated PIVKA-II levels compared to those with lower body fat [14]. These findings suggest that vitamin K may be stored and accumulated in adipose tissue and that increased body fat may be associated with VKD. In mothers with prepregnancy obesity, the sequestration of fat-soluble vitamins in adipose tissue may lead to a state of subclinical VKD, potentially increasing the risk of VKD in the fetus and the neonate at birth.

Maternal prepregnancy BMI showed a weak positive correlation with neonatal PIVKA-II levels on day 0 (before vitamin K administration). To the best of our knowledge, no previous studies have reported an association between maternal prepregnancy BMI and neonatal PIVKA-II concentrations. Dahlberg et al. investigated the prevalence of subclinical VKD using PIVKA-II in 35 perioperative neurosurgical patients and reported a positive correlation between BMI and PIVKA-II levels (r = 0.62, $P < 0.001$) [26]. In the present study, the correlation coefficient between maternal prepregnancy BMI and neonatal PIVKA-II levels on day 0 of life was r = 0.285, which is lower than the correlation reported by Dahlberg et al. in adult neurosurgical patients (r = 0.62). This weaker correlation may be attributed to the nature of our analysis, which examined the intergenerational relationship between maternal BMI and neonatal PIVKA-II levels, as opposed to the direct relationship between an individual's BMI and PIVKA-II levels in previous studies. Furthermore, our cohort included mothers with comorbid conditions, such as malnutrition and gastrointestinal diseases—known risk factors for VKD [27]—which may be associated with elevated PIVKA-II levels despite low maternal BMI, potentially confounding the observed association. Consistent with this, when these six cases were excluded from the analysis, the correlation between maternal BMI and neonatal PIVKA-II levels improved (Spearman's rank correlation coefficient = 0.310, $P < 0.0001$; unpublished data).

Our findings indicate that maternal prepregnancy obesity is an independent risk factor for neonatal VKD immediately after birth, suggesting the possibility of identifying infants at an increased risk for VKDB as early as the fetal period. In pregnancies complicated by maternal obesity, assessing maternal coagulation status antenatally and considering vitamin K supplementation on a case-by-case basis may be reasonable, given the observational links between

higher adiposity and lower vitamin K status (e.g., higher PIVKA-II) in adults and the limited placental transfer of vitamin K [14,26,28]. However, to our knowledge, no trials have shown that antenatal vitamin K supplementation in mothers with obesity improves neonatal clinical outcomes or reduces VKDB. Although supplementation lowered cord PIVKA-II among women who were receiving enzyme-inducing antiepileptic drugs [29] and a recent RCT demonstrated improved maternal and neonatal coagulation parameters following antenatal vitamin K administration before elective cesarean sections [30], systematic reviews and policy statements have concluded that prenatal supplementation does not reduce neonatal bleeding in the general population [1,31]. Prospective trials are needed to determine whether targeted antenatal strategies against maternal obesity improve neonatal outcomes.

This was a single-center retrospective observational study involving a limited number of patients with VKD. Detailed data regarding maternal nutritional intake during pregnancy and vitamin K kinetics in the body were not available. Further confirmation through large-scale prospective studies incorporating these factors is warranted. Moreover, because this study assessed VKD only at birth, it cannot address the potential long-term effects of maternal obesity on neonatal vitamin K status or the risk of VKDB during infancy. Previous studies have indicated that maternal and neonatal PIVKA-II levels do not necessarily correlate. For example, Chuansumrit et al. reported that neonates with overt vitamin K deficiency (PIVKA-II $\geq$5.0 AU/ml [equivalent to 5000 mAU/mL]) were often born to mothers with undetectable or minimal PIVKA-II levels, and the association between detectable maternal and neonatal PIVKA-II did not reach statistical significance [32]. This may partly explain why the absence of maternal PIVKA-II measurements in our study does not detract from the validity of our neonatal findings. Longitudinal follow-up studies are necessary to clarify these associations.

In conclusion, this study demonstrated that maternal prepregnancy obesity is independently associated with VKD in neonates at birth. Careful assessment of coagulation status may be warranted in infants born to obese mothers.

Declaration of generative AI and AI-assisted technologies in the writing process

Kazumichi Fujioka reports a relationship with Sanofi KK that includes: speaking and lecture fees. During the preparation of this work, the authors used ChatGPT (OpenAI) to improve the English translation of the manuscript. After using this tool, the author(s) reviewed and edited the content and take full responsibility for the content of the published article.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kazumichi Fujioka reports a relationship with Sanofi KK that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yu Masuda: Writing – original draft, Validation, Project administration, Investigation, Formal analysis, Data curation. **Mariko Ashina:** Writing – review & editing, Funding acquisition, Data curation. **Yukihito Imagawa:** Data curation. **Keisuke Shirai:** Data curation. **Yuki Nakata:** Data curation. **Takumi Kido:** Data curation. **Kenji Tanimura:** Writing – review & editing. **Kandai Nozu:** Writing – review & editing, Supervision. **Kazumichi Fujioka:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

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References

[1] Hand I, Noble L, Abrams SA. Vitamin K and the newborn infant. Pediatrics 2022;149:e2021056036. https://doi.org/10.1542/peds.2021-056036.
[2] Lane PA, Hathaway WE. Vitamin K in infancy. J Pediatr 1985;106:351–9. https://doi.org/10.1016/s0022-3476(85)80656-9.
[3] Kumar D, Greer FR, Super DM, Suttie JW, Moore JJ. Vitamin K status of premature infants: implications for current recommendations. Pediatrics 2001;108:1117–22. https://doi.org/10.1542/peds.108.5.1117.
[4] Sameshima T, Ashina M, Fukuda T, Kido T, Abe S, Watanabe Y, et al. Range of protein induced by vitamin K absence or antagonist-II levels in neonates at birth. Sci Rep 2024;14:921. https://doi.org/10.1038/s41598-024-51674-8.
[5] Ashina M, Fujioka K, Nishida K, Iijima K. Neonatal vitamin K deficiency in the son of a mother with short bowel syndrome. Pediatr Int 2018;60:991–2. https://doi.org/10.1111/ped.13684.
[6] Perrone S, De Bernardo G, Lembo C, Dell'orto V, Giordano M, Beretta V, et al. Vitamin K insufficiency and the prophylaxis strategy in term healthy infants: a multicentre study. Eur J Clin Investig 2024;54:e14141. https://doi.org/10.1111/eci.14141.
[7] Eventov-Friedman S, Klinger G, Shinwell ES. Third trimester fetal intracranial hemorrhage owing to vitamin K deficiency associated with hyperemesis gravidarum. J Pediatr Hematol Oncol 2009;31:985–8. https://doi.org/10.1097/MPH.0b013e3181c3a8bc.
[8] Minami H, Furuhashi M, Minami K, Miyazaki K, Yoshida K, Ishikawa K. Fetal intraventricular bleeding possibly due to maternal vitamin K deficiency. Fetal Diagn Ther 2008;24:357–60. https://doi.org/10.1159/000163078.
[9] Hirose M, Akiyama M, Takakura K, Noda Y. Active Crohn disease with maternal vitamin K deficiency and fetal subdural hematoma. Obstet Gynecol 2001;98:919–21. https://doi.org/10.1016/s0029-7844(01)01331-x.
[10] Renzulli P, Tuchschmid P, Eich G, Fanconi S, Schwöbel MG. Early vitamin K deficiency bleeding after maternal phenobarbital intake: management of massive intracranial haemorrhage by minimal surgical intervention. Eur J Pediatr 1998;157:663–5. https://doi.org/10.1007/s004310050907.
[11] Lippi G, Franchini M. Vitamin K in neonates: facts and myths. Blood Transfus 2011;9:4–9. https://doi.org/10.2450/2010.0034-10.
[12] Liu L, Chen CH, Rong SW, Lin SZ, Cai NL, Ao D. Antenatal steroid as an independent risk factor for vitamin K2 deficiency in newborns: a Chinese single-center, retrospective study. Saudi Med J 2023;44:788–94. https://doi.org/10.15537/smj.2023.44.8.20230084.
[13] Kimmons JE, Blanck HM, Tohill BC, Zhang J, Khan LK. Associations between body mass index and the prevalence of low micronutrient levels among US adults. MedGenMed 2006;8:59.
[14] Shea MK, Booth SL, Gundberg CM, Peterson JW, Waddell C, Dawson-Hughes B, et al. Adulthood obesity is positively associated with adipose tissue concentrations of vitamin K and inversely associated with circulating indicators of vitamin K status in men and women. J Nutr 2010;140:1029–34. https://doi.org/10.3945/jn.109.118380.
[15] Belle M, Brebant R, Guinet R, Leclercq M. Production of a new monoclonal antibody specific to human des-gamma-carboxyprothrombin in the presence of calcium ions. Application to the development of a sensitive ELISA-test. J Immunoassay 1995;16:213–29. https://doi.org/10.1080/15321819508013559.
[16] Itabashi K, Miura F, Uehara R, Nakamura Y. New Japanese neonatal anthropometric charts for gestational age at birth. Pediatr Int 2014;56:702–8. https://doi.org/10.1111/ped.12331.
[17] Card DJ, Gorska R, Harrington DJ. Laboratory assessment of vitamin K status. J Clin Pathol 2020;73:70–5. https://doi.org/10.1136/jclinpath-2019-205997.
[18] Kuitunen I, Huttunen TT, Ponkilainen VT, Kekki M. Incidence of obese parturients and the outcomes of their pregnancies: a nationwide register study in

Finland. Eur J Obstet Gynecol Reprod Biol 2022;274:62–7. https://doi.org/10.1016/j.ejogrb.2022.05.006.
[19] Bodnar LM, Catov JM, Roberts JM, Simhan HN. Prepregnancy obesity predicts poor vitamin D status in mothers and their neonates. J Nutr 2007;137:2437–42. https://doi.org/10.1093/jn/137.11.2437.
[20] Traber MG, Kayden HJ. Tocopherol distribution and intracellular localization in human adipose tissue. Am J Clin Nutr 1987;46:488–95. https://doi.org/10.1093/ajcn/46.3.488.
[21] Virtanen SM, van't Veer P, Kok F, Kardinaal AF, Aro A. Predictors of adipose tissue carotenoid and retinol levels in nine countries. The EURAMIC study. Am J Epidemiol 1996;144:968–79. https://doi.org/10.1093/oxfordjournals.aje.a008867.
[22] Parker RS. Carotenoids in human blood and tissues. J Nutr 1989;119:101–4. https://doi.org/10.1093/jn/119.1.101.
[23] Blum M, Dolnikowski G, Seyoum E, Harris SS, Booth SL, Peterson J, et al. Vitamin D(3) in fat tissue. Endocrine 2008;33:90–4. https://doi.org/10.1007/s12020-008-9051-4.
[24] Ravera M, Nickolas T, Plebani M, Iervasi G, Aghi A, Khairallah P, et al. Overweight-obesity is associated with decreased vitamin K2 levels in hemodialysis patients. Clin Chem Lab Med 2021;59:581–9. https://doi.org/10.1515/cclm-2020-0194.
[25] Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690–3. https://doi.org/10.1093/ajcn/72.3.690.
[26] Dahlberg S, Nilsson CU, Kander T, Schött U. Detection of subclinical vitamin K deficiency in neurosurgery with Pivka-II. Scand J Clin Lab Investig 2017;77:267–74. https://doi.org/10.1080/00365513.2017.1303190.
[27] Araki S, Shirahata A. Vitamin K deficiency bleeding in infancy. Nutrients 2020;12:780. https://doi.org/10.3390/nu12030780.
[28] Mandelbrot L, Guillaumont M, Leclercq M, Lefrère JJ, Gozin D, Daffos F, et al. Placental transfer of vitamin K1 and its implications in fetal hemostasis. Thromb Haemost 1988;60:39–43. https://doi.org/10.1055/s-0038-1647631.
[29] Cornelissen M, Steegers-Theunissen R, Kollée L, Eskes T, Motohara K, Monnens L. Supplementation of vitamin K in pregnant women receiving anticonvulsant therapy prevents neonatal vitamin K deficiency. Am J Obstet Gynecol 1993;168:884–8. https://doi.org/10.1016/s0002-9378(12)90839-x.
[30] Aziz RAA, Khalifa EM, Talaat BA, Abouahmad EA, Ahmed HH. Maternal and neonatal benefits of prophylactic administration of vitamin K before elective cesarean section; a randomized control trial. Annals Neonatol J 2023;5:42–58.
[31] Shahrook S, Ota E, Hanada N, Sawada K, Mori R. Vitamin K supplementation during pregnancy for improving outcomes: a systematic review and meta-analysis. Sci Rep 2018;8:11459. https://doi.org/10.1038/s41598-018-29616-y.
[32] Chuansumrit A, Plueksacheeva T, Hanpinitsak S, Sangwarn S, Chatvutinun S, Suthutvoravut U, et al. Prevalence of subclinical vitamin K deficiency in Thai newborns: relationship to maternal phylloquinone intakes and delivery risk. Arch Dis Child Fetal Neonatal Ed 2010;95:F104–8. https://doi.org/10.1136/adc.2009.173245.