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Original Article

Fetal Growth Cut-Off Point to Predict Neonatal Outcome in Pregnancy with Normal and Deficient Vitamin D Levels: Intergrowth-21, World Health Organization Fetal Growth Curve, and Hadlock's Estimated Fetal Weight

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Abstract

Purpose : Analyze the cut-off point of fetal growth based on the Intergrowth-21, World Health Organization (WHO), and Hadlock's estimated fetal weight (EFW) in pregnant women with normal or deficient vitamin D levels to predict neonatal outcomes.

Methods : This cross sectional study to develop a diagnostic test, included 120 of pregnant women who completed follow up until children aged 2 years, divided into normal and deficient vitamin D group. Ultrasound and maternal vitamin D level examined during the second trimester of pregnancy. EFW was calculated using Hadlock's formula and plotted on the Intergrowth-21 and WHO curves. The reference standards were the neonatal outcome, LBW, stunting, and neurocognitive impairment. Significant odds ratio (OR) value and area under the curve (AUC) of 0.6 are used to determine the cut-off point to be used.

Results : Fetal growth curve was based on the WHO at the 5th percentile to predict LBW to have an AUC of 0.6 and OR of 6, 95% confidence interval (CI) of 1.36–26.45. The AUC for predicting LBW based on Intergrowth and Hadlock were 0.45 and OR not significant. As well as the AUC estimated stunting based on Hadlock, the Intergrowth-21 and the WHO fetal growth curves is <0.6 with OR not statistically significant. The AUC predicted neurocognitive impairment based on WHO's chart was 0.6 but OR not statistically significant.

Conclusion : The WHO fetal growth curve can be used to predict LBW. The cut-off point of the fetal growth curve and which percentile is determined by the neonatal outcome.

Keywords : Fetal growth curve Cut-off Point, 25(OH)D, Stunting, Neurocognitive impairment

INTRODUCTION

Guidelines for performing an ultrasound (USG) examination to assess the estimated fetal weight (EFW) were published by the International Society of Ultrasound in Obstetrics and Gynecology, but plotting the growth curve during biometric measurements or EFW to determine the need for close monitoring is very important.[1] Fetal growth charts of normal pregnancies in a large population were published by several studies.[2–4] However, more specific fetal growth charts are needed concerning neonatal outcomes, especially low birth weight (LBW) infants, stunting, and neurocognitive impairment of children in special populations, as well as pregnant women with normal and deficient vitamin D levels.[5]

Vitamin D is a micronutrient that has calciotrophic (skeletal) and non-calciotrophic (extraskeletal) biological actions. Calciotrophic biologic action is important for calcium homeostasis regulation, which in turn contributes to intrauterine-initiated bone growth that contributes to fetal growth.[6] The main sources of vitamin D are sunlight and food.[7] Vitamin D deficiency is expressed by the 25-hydroxy vitamin D (25(OH)D) level in the blood. Vitamin D deficiency is a public health problem worldwide, especially concerning these two biological actions.[8]

Vitamin D deficiency during pregnancy affects the fetal growth and the bones of the child because of the calciotrophic biologic action of vitamin D. Research on vitamin D deficiency during pregnancy on fetal growth and birth weight gives inconclusive results.[9–12] A study linked vitamin D deficiency during pregnancy with the incidence of stunting, associated with fetal and child growth in the First Thousand Days of Life.[13]

Stunting is a condition in children with body length based on age and z score of <−2 according to the World Health Organization (WHO). Intrauterine fetal growth (IUGR) is one of the factors that influence the incidence of stunting in Indonesia.[14] The 2018 Basic Health Research data reported a 29.2% incidence of stunting in children aged 2 years and 30.8% in children aged 5 years.[15] This incidence decreased to 37.2% in children under 5 years old in 2013.[16] The 2019 Indonesian Toddler Nutrition Status Survey reported a decline in stunting incidence by 27.67%. These incidences have not met the WHO standard, which states that the incidence of stunting should be <20%, although it has decreased.[17]

One of the effects of vitamin D deficiency during pregnancy, as a non-calciotrophic biologic action, is the nervous system's development and function. Neurodevelopment includes cell differentiation and synaptic formation. Neurological functions include gene expression, metabolic regulation, neurotrophic-neurotoxicity, and a protective role against brain inflammation. Research on the relationship between maternal vitamin D status during pregnancy and children's cognitive function remained lacking. A study revealed that vitamin D levels during normal pregnancy affect the neurocognitive function of children.[18] Therefore, analyzing the cut-point of EFW in the second and third trimesters of pregnancy (based on Intergrowth 21, WHO, and Hadlock) is necessary in particular cases with vitamin D deficiency, LBW, stunting, and neurocognitive impairment.

METHODS

Research subject

This retrospective cohort study aimed to develop a diagnostic test, included 385 participants of the First 1000 Days of Life Medical Faculty Diponegoro University's research. A total of 120 pregnant women who had normal (n = 60) and deficient vitamin D (n = 60) levels had complete data until the child was 2 years old. The cut-off point was determined based on maternal vitamin D levels, LBW, stunting, and neurocognitive impairment. Sixty subjects, each group (normal and deficient vitamin D consist 30, conducted Capute Scale examination. The inclusion criteria included normal and singleton pregnancies. Exclusion criteria were fetal congenital abnormalities and premature birth. The data for children included gender, birth weight, stunting, and neurocognitive impairment when the child age 2 years old. Other data such as age, weight, height, body mass index, education and socioeconomic status of the mother were also collected.

Fetal growth classification

USG examination to assess EFW is conducted by obstetrics and gynecology specialists who have a basic USG examination certification from the Indonesian Obstetrics and Gynecology Association. The examining physician was blinded from the maternal vitamin D levels and fetal outcomes upon examination. The examination was conducted in the second trimester of pregnancy. The USG parameters assessed included biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL), and EFW according to Hadlock 1984.[19] Fetal growth cut-off point according to growth chart and EFW was assessed by reference standard maternal vitamin D levels and neonatal outcomes. Neonatal outcomes include LBW, stunting, and neurocognitive impairment when the child aged 2 years old. Fetal growth charts used Intergrowth-21 and WHO.[20]

Reference standard: Maternal vitamin D levels and fetal outcomes

Vitamin D levels were assessed from maternal blood 25(OH)D levels during the second trimester with a cut-off point of 20 ng/ml. Fetal outcomes were assessed for LBW, wasting or stunting, and neurocognitive disorders when the child was 2 years old. LBW is a baby who is born weighing <2,500 g and is classified as normal and low. Criteria for classifying children age 2 years into stunting was according to the WHO. Neurocognitive impairment were considered on a full scale (part of the examination Capute Scale) if the score less than 75.

Statistical analysis

Descriptive analysis was used to assess the characteristics of the subject of the mother and child. The cut-off point is assessed based on the receiver operating characteristic (ROC) curve and calculated Youden's index for each neonatal outcome based on vitamin D levels during pregnancy. Odds ratio (OR), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were assessed. The percentile fetal growth chart or EFW was selected based on significant OR values and an area under the curve (AUC) of 0.6.

RESULT

A total of 120 pregnant women, including 60 pregnant women each with normal and deficient vitamin D levels. Table 1 shows the patient characteristics. The average age of the mother is 29(5) years, and 39% have obesity. The average gestational age at the USG examination is 22 weeks. The number of babies born to boys and girls was 59 and 61 babies, respectively. Eight neonates were born with LBW, 15 with a stunting, and 5 with suspected neurocognitive impairment.

Table 2 shows the patient characteristics based on maternal vitamin D levels and nepnata; outcomes. No significant difference was found between gestational age, EFW on USG, and birth weight based on maternal vitamin D levels, and fetal outcome (LBW, stunting, and neurocognitive disorders).

Figure 1 shows the ROC curves of fetal growth and maternal vitamin D levels. All AUC values based on

TABLE 1
Patient characteristics based on ultrasound examination

Characteristics	n (%)	Median (min–max)	Mean (SD)
Mother			29.87 (5.57)
Age (years)		30 (17–44)	60.14 (12.27)
Mother's weight at measurement (kg)		57.25 (40.9–102.5)	26.06 (4.97)
Maternal body mass index (kg/m^2)		25.48 (18.30–49.18)	25.48 (18.30–49.18)
Underweight	15 (12.5)		
Normal	66 (55)		
Overweight	39 (32.5)		
Education			
Elementary School	9 (7.6)		
Junior High School	28 (23.3)		
Senior High School	70 (58.3)		
Associate degree	7 (5.8)		
Bachelor degree	6 (5)		
Socioeconomic			
Middle	74 (61.7)		
Low	46 (38.3)		
Maternal vitamin D level (ng/ml)		19.59 (4.94–37.65)	19.60 (5.2)
Deficient	60 (50)		
Normal	60 (50)		
Child			
Gestational age at ultrasound (weeks)		22.5 (1627)	22.5 (1627)

TABLE 1. Continued.

Characteristics	n (%)	Median (min–max)	Mean (SD)
Gender			
Boy	59 (49.2)		
Girl	61 (50.8)		
How to give birth			
Vaginal	63 (52.5)		
Caesarean section	57 (47.5)		
Baby's birth weight (grams)		3045 (2000–3900)	3066 (408)
< 2500	8 (6.67)		
>2500	112 (93.3)		
Z score PB/U (2 years)		−1.1 (−3.46–2.56)	−1.04 (0.96)
Tall	2 (1.7)		
Normal	103 (85.8)		
Short	13 (10.8)		
Very short	2 (1.7)		
Neurocognitive			
Suspected impairment	5 (1.9)		
Normal	57 (22.1)		

growth curves and EFW were 0.5.

Figure 2 shows the ROC curve of fetal growth and LBW. The AUC value of fetal growth curve based on the WHO growth curve was 0.6. Based on Youden's index, the cut-off fetal growth curve according to the WHO growth curve is the 5th percentile.

Figures 3 and 4 show the ROC curves of fetal growth and neonatal outcomes in terms of stunting and neurocognitive impairment at 2 years of age. The AUC value was 0.6 for neurocognitive disorders based on the WHO growth curve. Based on Youden's index, the cut-off fetal growth curve according to the WHO growth curve is the 35th percentile for neurocognitive impairment.

Table 3 shows the sensitivity, specificity, PPV, and NPV values for each fetal growth chart to predict maternal vitamin D and fetal outcomes. High sensitivity and NPV values on the Intergrowth-21 and fetal growth charts of the WHO predict maternal vitamin D, with a significant OR value. Likewise, the specificity and high NPV values on the WHO fetal growth chart predict LBW, with a significant OR value. The sensitivity, specificity, and NPV values were high on all fetal growth charts to detect stunting and neurocognitive impairment at the age of 2 years, but without significant OR values.

DISCUSSION

Based on the AUC and OR value, the WHO fetal growth curve can predict LBW in children. The growth curve according to the WHO has high specificity and NPV, which is appropriate for making the diagnosis. The AUC value of 0.6 is congruent with other study results. The RADIUS study on 9,409 pregnant women concluded that the fetal growth curve based on Intergrowth-21 and WHO had an AUC of 0.5–0.59.[21] A study of 3,437 African-American pregnant women comparing eight fetal growth charts, including Intergrowth-21 and WHO could not predict a poor combined perinatal outcome at the 10th percentile (AUC of 0.55) and a sensitivity of only 22%.[22] The Intergrowth-21 growth curve at the 10th percentile had an AUC of 0.52 in 1054 pregnant women in the United States.[23] Another study revealed similar results when comparing EFW based on Hadlock and Intergrowth-21 growth curves.[24] A study on 10,366 pregnant women that compared Hadlock, Intergrowth-21, and WHO revealed an AUC value of 0.54.[5]

Ultrasound during second or third trimester obtain estimate of fetal weight. But, ultrasound examination in the second trimester has been done to evaluate fetal anatomy. So, ultrasound in second

TABLE 2
Patient characteristics based on maternal vitamin D levels and neonatal outcomes

Variables	n (%)	Gestational age (week)	Estimated fetal weight (grams)	Baby's birth weight (grams)
			Mean (standard deviation)	
Vitamin D levels				
Normal	60 (50%)	22.27 (2.34)	553.7 (199.82)	3090.92 (403.37)
Deficient	60 (50%)	22.52 (2.32)	550.25 (192.82)	3062.92 (416.38)
Baby's birth weight				
<2500	8 (6.67)	23.33 (1.80)	574.88 (187.455)	2182.50 (372.24)
>2500	112 (93.3)	22.32 (2.35)	550.34 (196.81)	3130.09 (330.93)
Category z scores children aged 2 years				
Stunting	15 (12.5)	22.93 (1.83)	569.53 (175.26)	3018.33 (437.38)
Normal	105 (87.5)	22.31 (2.39)	549.47 (198.9)	3073.86 (406.63)
Neurocognitive				
Impairment	5 (8.06)	23.2 (3.34)	503.80 (121.08)	3208.4 (286.78)
Normal	57 (91.94)	22.28 (2.34)	536.58 (191.57)	3061.05 (409.58)

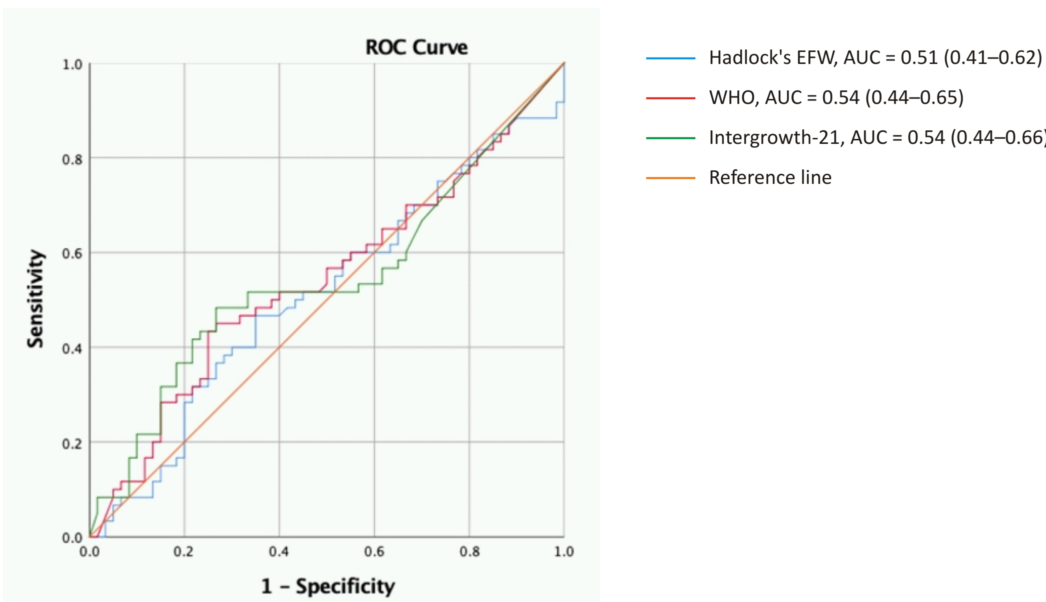

Figure 1. ROC curve of fetal growth based on maternal vitamin D levels

trimester is undergone for many more pregnant women than third trimester, especially in mid second trimester (18 – 22 weeks of gestation). Intrauterine fetal growth restriction in the mid second trimester of pregnancy related with neonatal outcomes. Fetal growth is linked to the placenta. The placenta is the organ that connects the fetus and the uterus. Various nutrients, hormones, and other endogenous metabolites from the mother will be transported via the placenta to the fetus. The cell that lines the outermost layer of the placenta is the syncytiotrophoblast, which is the smallest unit cell in the placenta and plays a role in fetal growth.[25] Vitamin D receptor is previously reported in trophoblasts; thus, vitamin D plays a role in fetal growth. The role of vitamin

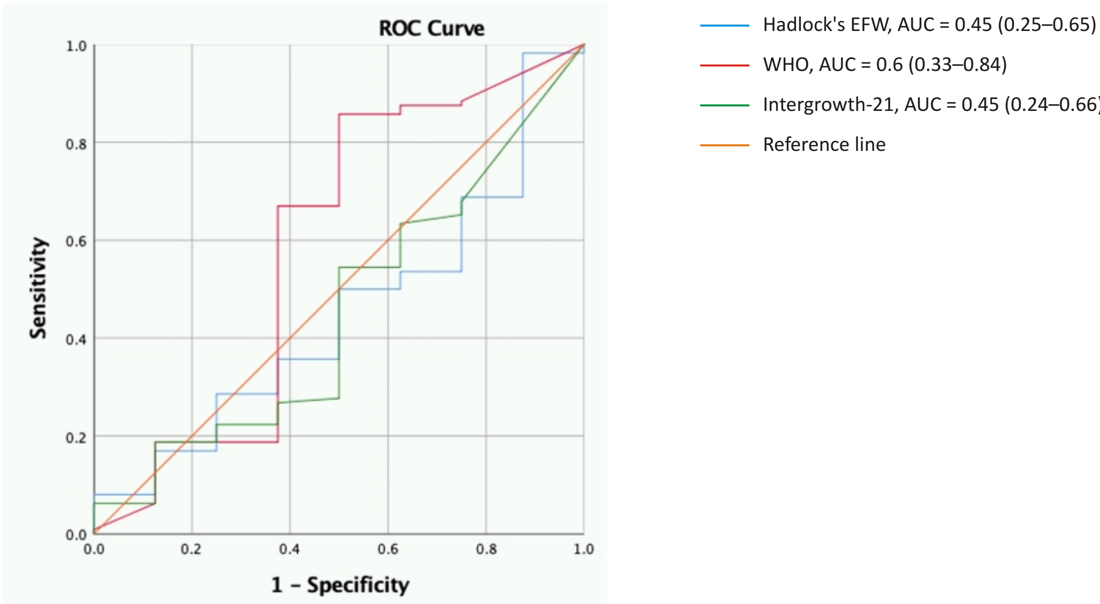

Figure 2. ROC curve of fetal growth and LBW

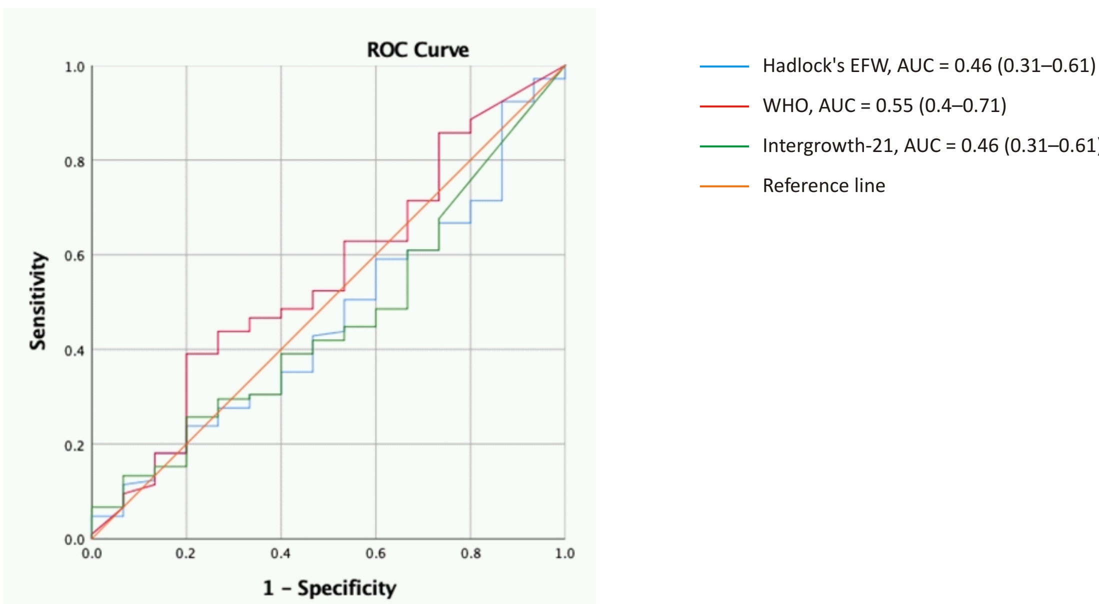

Figure 3. ROC curve of fetal growth and LBW

D during pregnancy on fetal growth includes calcium metabolism[26] and bone growth, as well as altered placental function.[27] Therefore, this study was conducted on specific participants, including pregnancies with normal and deficient vitamin D levels.

A study in Indonesia revealed that vitamin D deficiency in the first trimester was associated with low fetal BPD and AC.[28] Other studies linked vitamin D deficiency to low FL measures.[29] One study in Iraq found that vitamin D deficiency affected the weight and anthropometry of newborns.[30] Studies in Singapore revealed that vitamin D levels did not affect the anthropometry of newborns and postnatal, but this was because the incidence of vitamin D deficiency was only 1.6%.[31] Additionally, meta analysis studies supported the hypothesis that vitamin D deficiency is associated with LBW.[32] A study in Kenya linked vitamin D deficiency to stunting. A prospective cohort study in India included 250 primigravidas with normal pregnancies and examined vitamin D levels at 34 weeks of gestation. The

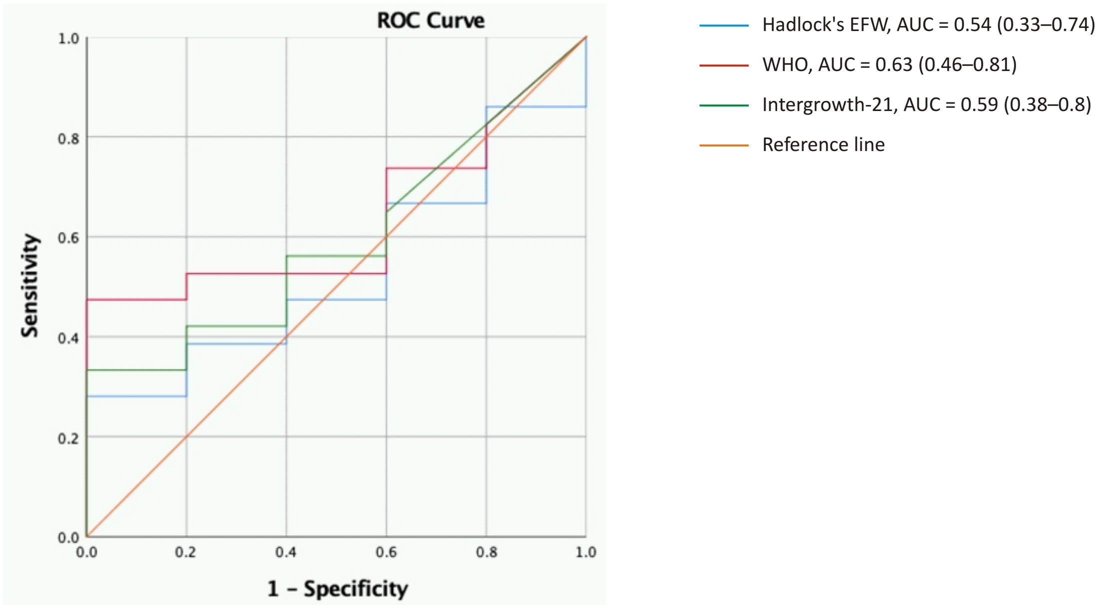

Figure 4. ROC curve of fetal growth and neurocognitive impairment at 2 years of age

study concluded that vitamin D deficiency affects fetal FL and birth length, but does not affect BPD and birth weight.[33] Another study revealed different results, no relationship was found between maternal vitamin D levels with birth weight, body length, and HC.[34]

Research on the effect of fetal growth on the incidence of stunting and birth weight remained lacking. The incidence of stunting is related to bone growth that supports the child's height. Bone is the greatest nutritional priority compared to fat and muscle because bone plays an important role in maintaining mineral balance, providing structural support, and hematopoiesis.[35] A prospective British cohort study that included 628 pregnancies who are followed up to 4 years of age concluded that fetal growth (AC measurement) in the second half of pregnancy was associated with bone mineralization at birth, and growth in children younger than 2 years of age was associated with bone mineralization at 4 years of age.[36] A prospective cohort study by the same investigators in 380 pregnancies revealed that fetal growth (AC and FL measurements) in the second half of pregnancy was associated with bone mineralization at 4 years of age.[37] A prospective cohort study of 399 females with normal pregnancies revealed that birth weight correlated with child length at 6, 12, and 24 months of age; FL at 20 weeks of measurement correlated with infant FL at birth; infant FL at birth correlated with FL at 6 months and 24 months.[38] The mechanism of the effects of bone growth on fetal growth and birth weight remained unknown but may be related to leptin, growth hormone, and cortisol.[39]

Stunting is also associated with neurocognitive disorders in children. Pregnancy is a critical phase of brain growth and development which includes the growth and differentiation of neuron cells, neuron migration, dendritic arborization, synaptogenesis, gyrus formation, myelination, and apoptosis. A cross-sectional study was conducted on 170 normal pregnancies and children aged 3–30 years who had undergone magnetic resonance imaging (MRI) 1022 times. The results revealed that the greater the birth weight of the baby, the greater the total volume of the brain, cerebral cortex, white matter, and gray matter. The volume of the cerebral cortex is related to the surface area of the cerebral cortex. The hypotheses included the following: a migration of neurons from the subventricular area to the cortex when RFW can be easily influenced by external stimuli, occurs in the second trimester of pregnancy. Hence, EFW disruption will affect the migration of neurons. The prefrontal area of the cortex is associated with later neurocognition.[40] A study of 756 neonates who underwent MRI at 2 weeks of age concluded an association between the increase of 500 grams of birth weight and the 4% increase in intracranial volume, which is the total volume of gray matter, white matter, and cerebrospinal fluid. MRI examination in early neonates is associated with neurocognitive disorders.[41]

Therefore, this is the first study that included the population of pregnant women with normal and deficient vitamin D levels to know the graph and percentile of fetal growth that will be chosen to predict LBW because previous research publications are unavailable. Additionally, the observation time is sufficient because at the time of first 1000 days. However, further research is needed with a bigger sample size before its application in daily practice.

TABLE 3
Fetal growth cut-off point for predicting maternal vitamin D levels and neonatal outcomes (OR, sensitivity, specificity, PPV and NPV)

Cut-off point	Proportion < cut-point n (%)	OR (95%IK)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Vitamin D Intergrowth-21	75 (62.5)	2.57 (1.25.52)	73.33 (60.34–83.93)	59.21 (47.33–70.35)	58.67 (50.98–65.95)	73.77 (63.99–81.66)
WHO	79 (65.8)	2.29 (1.05–4.98)	75 (62.14–85.28)	43.33 (30.59–56.76)	56.96 (50.38–63.31)	63.41 (50.62–74.56)
EFW	54 (45)	1.14 (0.56–2.35)	46.67 (33.6–760)	56.67 (43.24–69.41)	51.85 (42.02–61.54)	51.52 (43.45–59.50)
LBW Intergrowth-21	85 (70.8)	0.38 (0.9–1.6)	50 (15.78–4.30)	27.68 (19.64–36.93)	4.71 (2.39–9.06)	88.57 (78.46–94.28)
WHO	20 (16.7)	6 (1.36–26.45)	50 (15.78–4.30)	85.71 (77.84–91.61)	20 (9.85–36.40)	96 (92.28–97.97)
EFW	54 (45)	0.38 (0.07–1.99)	25 (3.19–65.05)	53.57 (43.9–63.05)	3.7 (1.13–11.49)	90.91 (86.61–93.92)
Stunting Intergrowth-21	59 (49.2)	0.47 (0.15–1.47)	33.33 (11.82–61.62)	48.57 (38.75–8.53)	8.47 (4.23–16.25)	83.61 (77.22–88.74)
WHO	76 (63.3)	2.56 (0.68–9.64)	75 (47.62–92.37)	71.93 (58.46–83.03)	42.86 (31.21–55.36)	91.11 (60.91–82.39)
EFW	32 (26.7)	0.38 (0.08–189)	13.33 (1.66–40.46)	71.43 (61.79–79.82)	6.25 (1.74–20.06)	85.23 (82.06–87.92)
Neurocognitive Intergrowth-21	41 (66.1)	2.16 (0.23–20.67)	80 (28.36–99.49)	35.09 (22.91–48.87)	9.76 (6.28–14.85)	38.71 (26.60–51.93)
WHO	35 (56.5)	0.85 (0.7–40.9)	100 (47.82–100)	47.82 (33.98–61.03)	14.29 (11.53–17.57)	–
EFW	41 (66.1)	2.16 (0.23–20.67)	80 (28.36–99.49)	35.09 (22.91–48.87)	9.76 (6.28–14.85)	95.24 (76.98–99.17)

CONCLUSION

The WHO fetal growth curve can be used to predict LBW. The cut-off point of the fetal growth curve and which percentile is determined by the neonatal outcome.

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