Research Article

Dynamic of maternal vitamin 25(OH)D and 1,25(OH)2D level throughout pregnancy in small for gestational age infant: a cohort study of vitamin D impact on pregnancy in West Java- Indonesia

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ABSTRACT

Background: Different reports of Vitamin 25(OH)D and vitamin 1,25(OH)2D level in pregnancy showed different impact to pregnancy outcome. Those different results suggested a possible dynamic of vitamin D level throughout pregnancy which play role in pregnancy outcome. In this study, we describe different proportion of vitamin 25OH D and 1,25 OH D deficiency during the first trimesteruntil throughout pregnancy and its distribution according to infant birth weight.

Methods: A nested cohort study collected consecutive data from infant with small for gestational age (SGA) and retrospectively traced maternal vitamin 25(OH)D and 1,25(OH)2D distribution during the first, second and third trimester of pregnancy. This study is a part of cohort study of vitamin D impact on pregnancy in West Java-Indonesia. Level of vitamin 25(OH)D and Vitamin 1,25(OH)2D were classified into severe, moderate deficiency, and optimal.

Results: Vitamin 1,25(OH)D severe deficiency occured in 70.5%, 67.8%, and 31.3% subjects in the first, second, and third trimester, respectively. Vitamin 25(OH)D deficiency occured in 13.2%, 8%, and 14.7% subjects in the first, second, and third trimester. The higher proportion of 1,25(OH)D severe deficiency pattern compared to 25(OH)D severe deficiency also occured inSGA and non SGAinfant throghout pregnancy. Moderate deficiency of 25(OH) occured in higher proportion in non SGA infant compared to SGA infant. Moderate deficiency occured in higher proportion for 25(OH)Dthroughout pregnancy.

Conclusion: Vitamin 1,25(OH)2D severe deficiency occured in higher proportion in SGA infant throughout three trimester of pregnancy compared to 25(OH)D. Non SGA infant tend to experience moderate deficiency for 1,25(OH)D and 25(OH)D.

Keyword : infant birth weight, , trimester of pregnancy, maternal, vitamin 25(OH)D level, vitamin 1,25(OH)2D level.

INTRODUCTION

Institute of Medicine (IOM) set vitamin D deficiency by serum 25(OH)D below 20 ng/ml as a cut-off to minimize majority of global population being vitamin D deficient.[1] However, this effort seemed remain challenges for many population. Aside from normal value variation due to skin pigmentation, nutritional status, and ultraviolet Bexposure, some determinants characterised vitamin D status.[1,2] In the Southeast Asia country, low vitamin D status attributable to be female, younger age, living in an urban area and being less physically active.[3]Certain physiologic condition, such as pregnancy can even furtherlowered vitamin D level.[1,2]Hong-Bi, et al reported a mean maternal vitamin 25(OH)D level during pregnancy in China was as low as 16.17±6.27 ng/mL.[4]Our initial report signified high prevalence of vitamin D deficiency accounted for 75% from the studypopulation.As many as 60 (20.5%) pregnant women had vitamin D level lower than 8.1 ng/ mL. Maternal sera vitamin 25(OH)D level was reported in the mean (SD) of 14.7(6.5) ng/ml.[5] The active form of vitamin D, however, is in the form of 1,25OH D, hence observing this active form will give better nuance of the dynamic of vitamin D during pregnancy and its impact to pregnancy outcome. Small for gestational age (SGA) has been reported as an outcome of vitamin D deficiency in different countries.[6,7] There is limited report on how variation of both forms of 25(OH)D and 1,25(OH)D throughout pregnancy might affect pregnancy outcome.

In this report we describe the dynamic of vitamin 25(OH)D and vitamin 1,25(OH)2D in the first trimester, second, and the third trimester of pregnancy as well as its distribution according to the birth-weight outcome.

METHODS

This study was a part from the cohort study of vitamin D impact on pregnancy in West Java-Indonesia. The cohort of pregnant women were recruited from 4 regencies. The sample calculation, sample selection chart, exclusion and lost to follow up were described in previous report of our cohort.[5,8] In this current report, women who were completely followed up until giving birth was used as a population. Infants born with small for gestational age werefurther paired with a random selected control subjectsfrom this population. Mother-infant dyads were recruited consecutively and followed in every trimester by which 25(OH) vitamin D and 1,25 (OH) vitamin D level were measured. Characteristics includes maternal age, occupation, educational level, gestational age, parity, and infants birth weight and length.

Vitamin D measurements were performed using ELISA procedures.Determination of SGA babies was done after birth, which defined by birth-weight fell below 10th percentile at certain gestational age. Severe deficiency, moderate deficiency and optimal level of 25(OH)D and 1,25(OH)D were defined based on Kennel, et al.[2] Data was described using table and graphic. The protocol was approved by The Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran on June 2016.

Table 1 .Maternal and Neonatal Characteristics

	SGA	Normal
	(n=33)	(n=34)
Maternal characteristics		
Age		
• **<20 years**	2	2
• **20-34 years**	24	26
• **≥35 years**	7	6
Education		
• **No formal education/ elementary**	6	5
• **Middle school**	14	15
• **High school**	9	9
• **Diploma/bachelor**	4	5
Occupation		
• **Housewife**	28	21
• **Government officer**	3	6
• **Others**	2	7
Pre-pregnancy BMI (kg/m2)		
• **Underweight (<18.5)**	8	5
• **Normal (18.5-24.9)**	18	20
• **Overweight (≥25)**	7	9
Gestational age at delivery		
• **<37 weeks**	7	6
• **37-42 weeks**	26	28
• **>42 weeks**	0	0
Parity		
• **Nully-parity**	15	12
• **Multi-parity**	18	22
Neonatal characteristics		
• **Birth weight (gr) ; mean (SD)**	2388.13 (327.73)	3185.46 (323.2)
• **Birth length (cm) ; mean (SD)**	46.9 (2.51)	49.35 (2.04)

RESULTS

From total number of 317 pregnant women-subjects, we collected data on 203 mother-neonates dyads, in which 33 were considered small for gestational age, giving prevalence as much as 10%. A nested study was completed with 34 non-SGA control group. There are no difference between characteristic of the two groups. Maternal and infant characteristic for study subjects were in the table 1.

Deficiency of 1,25(OH) D and 25 (OH)D

Deficiency of 25(OH)D and 1,25(OH)D occured throughout first, second, and third trimester, accounting for 19% in all subjects for 25(OH)D and 70.8% for 1,25(OH)D in the first trimester. In the second trimester, 8% of all subjects deficient for 25(OH)D and 60.8% for 1,25(OH)D. In the third trimester 14.7%of all subjects deficient for 25(OH)D and 60.8% deficient for 1,25(OH)D.30.8%.

Severe Deficiency of 1,25(OH)2D and 25(OH)D in SGA infant

In SGA group, deficiency of 1,25(OH)2D always in higher proportion throughout the three trimesters compared to deficiency of 25(OH)D. This allowing normal level of 25(OH)D always in higher proportion throughout pregnancy compared to 1,25(OH)2D normal level.

High proportion of missing data in trimester 3, however, prevent adequate interpretation of the data in SGA group.

In the non SGA group, deficiency of 1,25(OH)2D also always in higher proportion throughout the three trimesters compared to deficiency of 25(OH)D

Moderate deficiency of 1,25(OH)2D and 25(OH)D

Moderate deficiency of 1,25(OH)2D shown different pattern compared to moderate deficiency of 25(OH)D either in SGA or in non SGA group. Moderate deficiency of 1,25(OH)2D was occured in lower frequency within SGA group compared to moderate deficiency of 25(OH)D. In other word, moderate deficiency 25(OH)D was higher compared to moderate deficiency 1,25(OH)2D in SGA group. In non SGA group, moderate deficiency of 25(OH)D was higher throughout the three trimester compared to moderate deficiency of 1,25(OH)2D.

Optimal level of vitamin 1,25(OH)2D and 25(OH)D

Optimal level of vitamin 1,25(OH)2D only noticed in the third trimester, suggested a compensation mechanism to increase the 1,25(OH)2D level during the third trimester. Vitamin 25(OH)D level did not show typical increase or decreased in the third trimester or thoughout the pregnancy.

Missing data in SGA group is high in third trimester.

Missing data profoundly shown in the third trimester for 1,25(OH)2D and 25(OH)D in SGA group accounted for 60.6% of the whole SGA data. In non SGA group, data missing was also noticed in the third trimester, but in smaller proportion and accounted for 29.4% data.

There are 4 missing data for vitamin 1,25(OH)2D and 3 missing data for vitamin 25(OH)D in the first trimester. In the second trimester, there are no missing data for vitamin 25(OH)D and for vitamin 1,25(OH)2D. Twenty out from 33 and 20 out from 34 data are missing in the third trimester account for vitamin 25(OH)D and vitamin 1,25(OH)2D, respectively.

Only 19out from33 proportion of mothers experienced deficient Vitamin 25(OH)D during the first trimester of pregnancy, however 23out from 34pregnant women experienced deficient Vitamin 1,25(OH)2D level starting in the first trimester and continued throughout the second trimester and lesser to the third trimester of pregnancy as shown in the figure 2. Deficiency of Vitamin 1,25(OH)2D signified during the three trimester.

The dynamic of Vitamin 25(OH)D and 1,25(OH)2D in both SGA and non SGA group was shown in figure 2

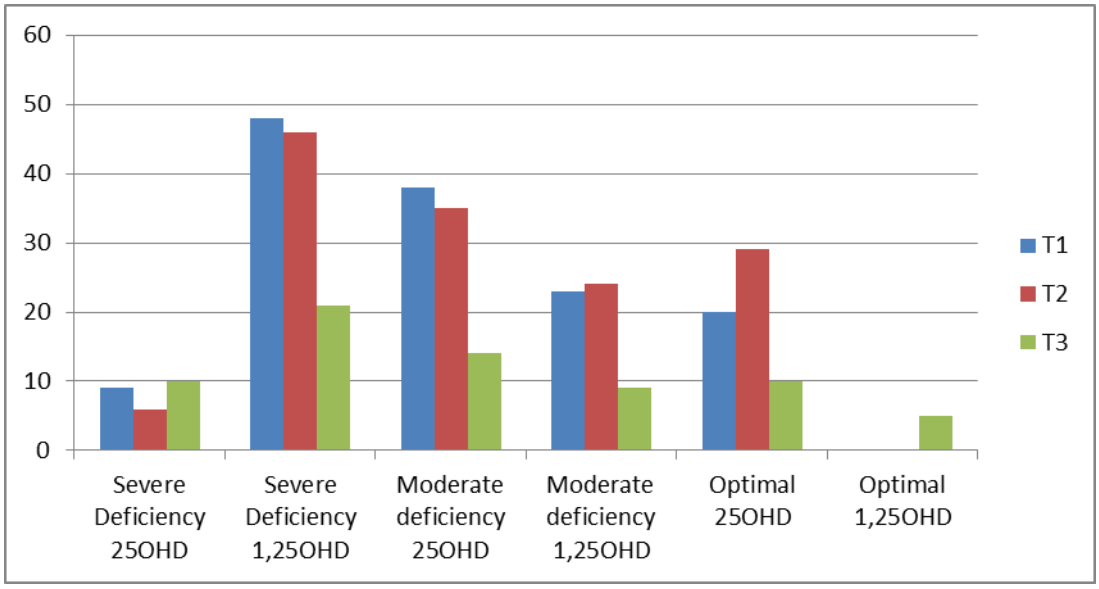

Figure 1. Proportion of subjects experience vitamin 25(OH)D and Vitamin 1,25(OH)2D deficiency and insuficiency throughout the pregnancy. T represent Trimester

		T1	T2	T3
SGA	Severe Deficiency 1,25OHD			
	Moderate deficiency 1,25OHD			
	Optimal 1,25OHD			
	Missing data 1,25OHD			
Non SGA	Severe Deficiency 1,25OHD			
	Moderate deficiency 1,25OHD			
	Optimal 1,25OHD			
	Missing data 1,25OHD			
SGA	Severe Deficiency 25OHD			
	Moderate deficiency 25OHD			
	Optimal 25OHD			
	Missing data 25OHD			
Non SGA	Severe Deficiency 25OHD			
	Moderate deficiency 25OHD			
	Optimal 25OHD			
	Missing data 25OHD			
	Legend	0	15	30

Figure 2. Dynamic of vitamin 25(OH)D and vitamin 1,25(OH)2D throughout three trimester of pregnancy according to infant SGA and non SGA status

DISCUSSION

During pregnancy, the 1,25(OH)2D regulates key target genes associated with implantation to ascertain placental implantation and development is successfully maintained throughout pregnancy. Vitamin 1,25(OH)2D affect fetal "imprinting" and influence pregnancy outcome as well as chronic condition in later life.[1]Observing

25(OH)D together with 1,25(OH)2D give perspective on how vitamin D level changes from time to time and might impact the pregnancy outcome.[9,10]Using definition of moderate vitamin D deficiency at the level 10-24ng/mL, severe deficiency at the level less than 10ng/mL, and normal level as 25-80ng/mL,[2] our study has shown that there are different pattern of vitamin 25(OH)D and vitamin 1,25(OH)2D throughout the pregnancy.

Data from our observation showed that deficient state of 1,25(OH)2Don first trimester in the SGA group continued on second trimester although there is a surge of level on third trimester. This is in opposed to physiologic phenomenon where vitamin D increased during first trimester and continued throughout pregnancy and lactation[11] in which we expect to see higher level of vitamin D. We, however, did not assess pre-gestational vitamin D level to confirm whether the current level is a result of increment or reduction from pre gestational level. In the other hand, a report from Switzerland found similar results from our study noticing low vitamin D level in the first trimester. This results was reported in the form of vitamin 25(OH)D, having prevalence similar to our in the whole cohort and around 30% prevalence of vitamin D deficient in the first trimester. Authors suggest possibility of relationship between the low vitamin D level in the first trimester and pregnancy outcome.[12]

The level increment at the third trimester possibly reflects compensation or delays, however, contributing factors and mechanism need to be elucidated. Deficient state of25(OH)Doccured in lower proportion compared to 1,25(OH)2Din SGA infant possibly reflects the immediate source of 25(OH)Dwhilst 1,25(OH)2Dneed further process[1] which physiologically occured in human body.

This dynamic pattern depicts the lacks of transformation from25(OH)D into 1,25(OH)2D possibly due to inability of enzyme CYPB27B for convertion.[1,8] Vitamin D deficiency significantly increased the risk of neonatal low birth weight (LBW) and small-for-gestational-age (SGA).[10,11,13]We have shown that both maternal 25(OH)Dand level in the second trimester of pregnancy was associated with low fetal biometry in the third trimester of pregnancy (in press). Further study is needed to see if maternal 25(OH)D and 1,25(OH)2D have an association with the activity of enzyme CYP24B1 which metabolized vitamin D1 into vitamin 25(OH)D and activity of enzyme CYP27B1 which converts 25(OH) vitamin D into 1,25(OH) vitamin D level. Vitamin D level during the second trimester of pregnancy (in press) showed that there is a possibility that the enzyme activity migt work in the placenta and bridged the less favorable of pregnancy outcome.

Impact of low vitamin D in pregnancy is well known and accepted, but the condition is rare and need large study samples to obtain confirming results, giving challenges for the study. In this cohort we found 33 out from 203 mother-infants dyads, which become limitation of the study.

Conclusion

There are different dynamic of vitamin 25(OH)D and vitamin 1,25(OH)2D level throughout pregnancy. In SGA group, deficient of vitamin 1,25(OH)2D level started to occur in the first trimester of pregnancy and persist in the second and third trimester. Level of 25(OH)D although low has a better level throughout pregnancy suggesting further study to elucidate the role of liver enzyme vitamin D-25-hydroxylase (CYP24R1) and 25(OH)D-1α-hydroxylase (CYP27B1) in the kidneyswhich convert both vitamin D to birthweight of the infant by the end of pregnancy.

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