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Vitamin D Deficiency and Gestational Diabetes Mellitus

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Abstract: ***We examined the association of second-trimester maternal plasma 25-hydroxyvitamin D (25[OH]D) during pregnancy with gestational diabetes mellitus (GDM) and also Studied various socio-demographic factors associated with Vitamin D deficiency among cases and controls. Methodology adopted was a case control study where 150 patients were included, 75 each in study group and control group. Observational studies provide conflicting evidence as to whether low serum 25-hydroxyvitmain D (25 (OH)D) levels are associated with GDM. Our study showed an inverse relationship between serum vitamin-D levels and Gestational diabetes mellitus and how diverse socioeconomic factors influenced the serum vitamin-D levels among antenatal women.***

1. Introduction

Pregnancy and childbirth and the associated complications are the leading causes of disability among women in the reproductive age group in the developing countries accounting for at least 18% of disease burden in this age group. (1)
Gestational Diabetes Mellitus (GDM) is an increasingly prevalent medical disorder in pregnancy which affects 2% to 20% (2) of all pregnancies depending on geographic region.

Prevalence of GDM among Urban, semi urban and rural was found to be – 17.8%, 13.8% and 9.9% respectively of pregnancies in southern part of India. (3)

Several reviews have been discussed regarding the Prevalence, risk factors and outcome of GDM and vitamin deficiency in pregnant women and based on which there is a need for interventional trials to test possible beneficial effects of vitamin D supplementation in pregnant women.

Aims and Objectives

- To Assess mid trimester vitamin D levels in women with GDM at gestational age of 24-28 weeks
- Evaluate association of low Vitamin D levels and GDM.
- Study socio-demographic factors associated with Vitamin D deficiency among cases and controls.

2. Materials and Method

This study is a ‘ Case control study, carried out over a period from September 2014 to August 2015, in the Department of Obstetrics and Gynaecology, in a tertiary care hospital’.

3. Study Population

150 antenatal women at 24-28 weeks of gestation
Women with GDM (cases): 75
Pregnant women without GDM (controls): 75

Sample group taken in the study were :

1) Women in second trimester at 24-28 weeks period of gestation with Two or more impaired values with 100 g of OGTT, diagnosed based on Carpenter and Coustan criteria (4).

100 g of oral glucose-OGTT

Fasting-95 mg/dl	(5.2 mmol/l)
1 h	-180 mg/dl (10 mmol/l)
2 h	-155 mg/dl (8.6 mmol/l)
3 h	-140 mg/dl (8.1 mmol/l)

2) Fasting plasma glucose levels >126mg/dl

Comparison group
Women in second trimester at 24-28 weeks period of gestation with euglycemic status.

Inclusion Criteria
Women at 24-28 weeks of gestation diagnosed with gestational diabetes mellitus.

Exclusion Criteria

- Women with pre-existing renal, heart, endocrinology disorders
- Women with overt diabetes mellitus
- Women on injectable insulin or hypoglycaemic drugs
- Women taking vitamin-D supplements.

Approval and Registration
Prior to enrolment ethical committee clearance was obtained from Hospital Ethical Committee.

Sample Size:
The sample size for each group is obtained from the formula,
Sample size =n=z2pq/E.
Where n is the sample size
p=Prevalence
q=1-p
E=allowable error
Total sample size = 150.

4. Methodology

Serum concentrations of vitamin D metabolites (25-hydroxyvitamin D 25[OH]vit D3) will be determined by radioimmunoassay kits (ELISA) at the biochemistry department, KMC, Mangalore.

2ml of venous blood samples will be collected; serum would be separated, and stored at −20°C until analysis. The treated samples would then be assayed using competitive-binding radioimmunoassay.

Study would require the use of two ELISA kits, (ELISA one kit-16000+tax) and results were reported based on the classification of vitamin-D levels ;

Vitamin-D Deficiency and its Values (5):

Vitamin–D levels	Interpretation
<10ng/ml	Severe deficiency
10-24ng/ml	Mild to moderate deficiency
25-80ng/ml	Normal levels
>80ng/ml	Toxicity possible

Various social demographic factors were studied using a self-reported questionnaire which included details based on diet, sunlight exposure, socioeconomic status (6) ,religions and skin colour (based on Fitzpatrick scale)

5. Results and Discussion

Total of 150 pregnant patients were taken for the study who fulfil the inclusion criteria of the study as mentioned earlier. Characteristics of the study population 150 singleton pregnancies admitted or came for routine antenatal visits in Lady Goshen Hospital from May 2015 to July 2016 at period of gestation between 24-28 weeks were included in study population and serum vitamin d was measured in these patients.

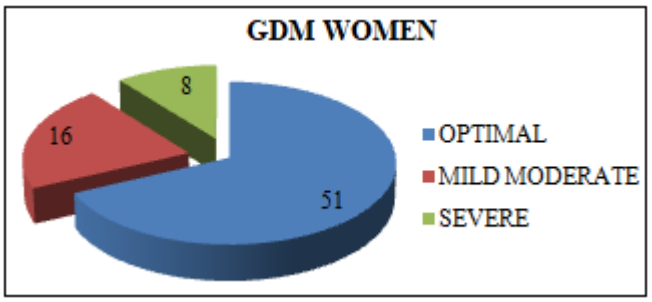
Category-	Cases	Control	Total
Optimal <25ng/ml	51 (68%)	53 (70%)	104
Mild/Moderate 10-24 ng/ml	16 (21%)	22 (30%)	38
Severe <10ng/ml	8 (10%)	0	8
Total	75	75	150

Out of 150 women, a total of 104 (69.3%) women were found to have optimal levels of vitamin-D. Majority of women under the study were belonging to this category, 38 (25%)were found to have mild-moderate deficiency and 8 (5.3%) were found to have severe deficiency of vitamin-D.

Among women with gestational diabetes mellitus, Hypovitaminosis was found among 24 women.

Severe deficiency were found among 10% of women with established diagnosis of GDM. (Mean value of vitamin-D was 3.5ng/ml)

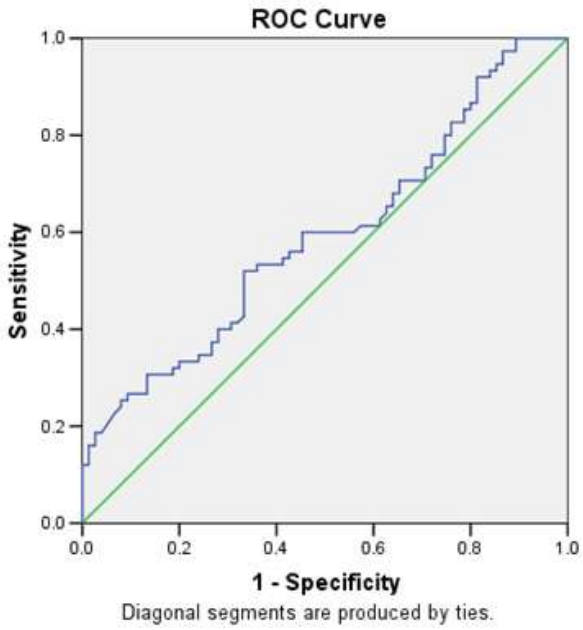
Optimal and mild to moderate category between cases and controls were comparable.



Statistical Analysis

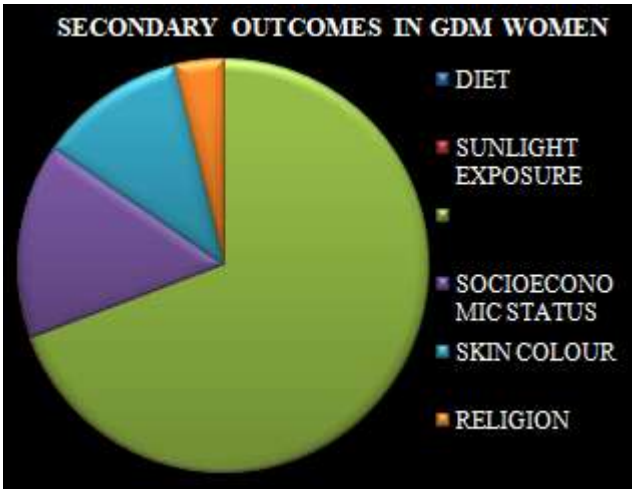
Groups	N	Mean	Standard Deviation	P value
Cases	75	29.14	13.14	0.007-HS-Fishers Exact Test
Control	75	35.33	14.8	

ROC curve: With 95% confidence interval, lower bound of 0.501 and upper bound of 0.683, Sensitivity of vitamin –D in relation to gestational diabetes mellitus was 99%; Specificity of vitamin-D was found to be 89%



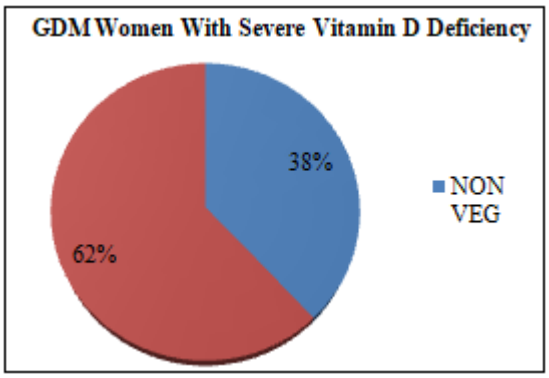
Secondary Outcomes and its Effect on GDM

Various sociodemographic features associated with Gestational diabetes mellitus and vitamin-D were studied using a self-reported questionnaire,



Diet Correlation with GDM

- Among women with gestational diabetes mellitus, 58.7 % of women consumed non vegetarian diet and 41.3% consumed vegetarian diet.
- 62.5% of GDM women with severe vitamin-D deficiency were found to be consuming vegetarian diet.
- 77% of women with GDM and 72 % of women in the control group having optimal levels of vitamin-D were found to consume a non-vegetarian diet.

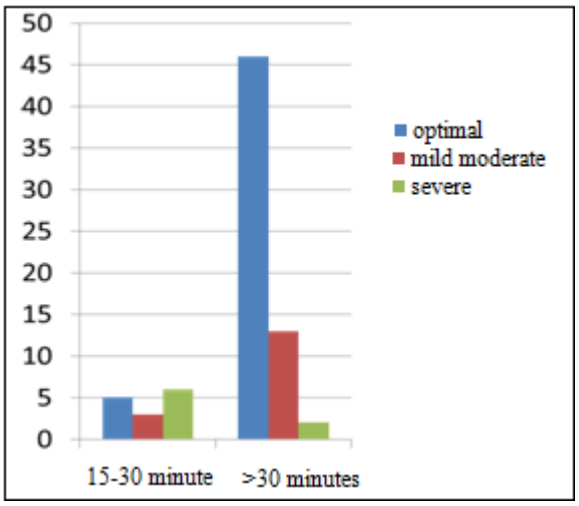


Effect of sunlight exposure on cases

Sunlight Exposure	cases-GDM women			
	Optimal	Mild-moderate	severe	Total
15-30 minute	5	3	6 (75%) P value= 0.001, HS	14
>30 minutes	46 (90%)	13	2	61

Severe vitamin-D deficiency among gdm (60%) were found among those with history of sunlight exposure less 30 minutes, it was found to be statistically significant ,p value =0.001

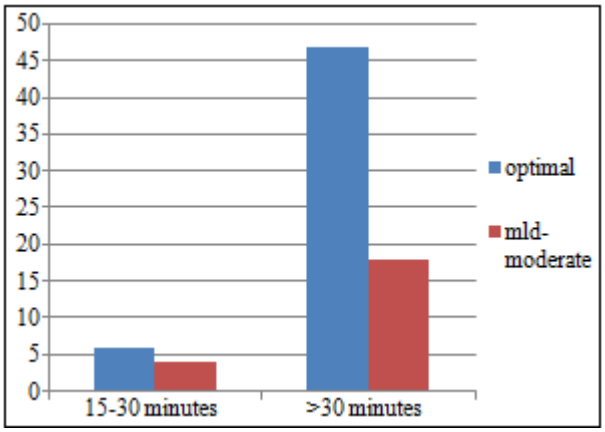
Among women with optimal levels of vitamin-D ,90% women had sunlight exposure of more than 30 minutes.



Effect of sunlight exposure on the control group

Sunlight Exposure	Controls		
	Optimal	Mild-moderate	Total
15-30 minute	6 (60%)	4 (40%)	10
>30 minutes	47 (72%)	18 (27%)	65

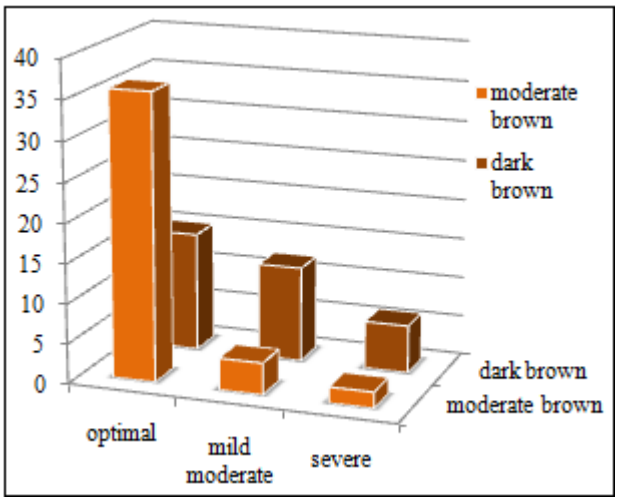
Among control group, 72% of women with optimal levels of vitamin-D had sunlight exposure more than 30 minutes, and p value was found to be highly significant p=0.001 HS



Study on skin colour variation among cases group:

On studying the skin colour among women with gestational diabetes mellitus in relation to vitamin-D Status, women with deficient levels of vitamin-D were found belonging to Fitzpatrick type 5 dark brown skin colour and it was found to be statistically significant =p value of 0.034

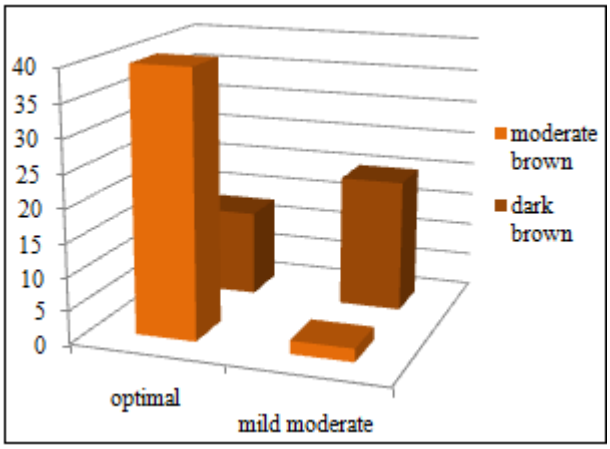
Skin colour	GDM (Cases)		
	optimal	Mild-moderate	severe
Moderate brown (type 4)	36 (70%)	4	2
Dark brown (type 5)	15	12	6 (75%) P value=0.034 sig



Study on skin colour variation among controls group

On studying the skin colour variation among women with optimal levels of vitamin-D , 76 % of them belonged to fitzpatrick type 4 (moderate brown) with a p value of 0.012

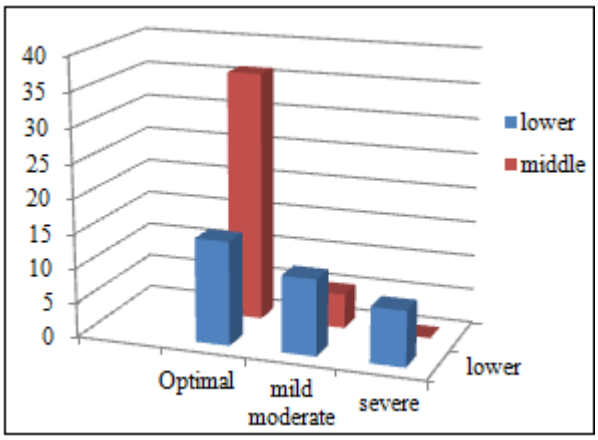
Skin colour	Controls	
	Optimal	mild-moderate
Moderate brown	40 (76%) P value=0.012 sig	2
Dark brown	13	20



Correlation of vitamin-D status and socioeconomic status among cases:

Among women with gestational diabetes mellitus, severe vitamin –D deficiency was found with those belonging to lower socioeconomic group, with a p value =0.001 Highly significant.

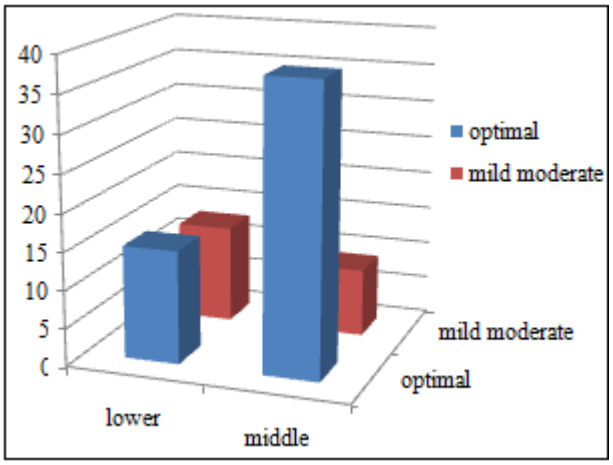
Socioeconomic status	Cases (GDM)-vitamin -D		
	optimal	Mild-moderate	Severe
Lower	15	11	8
Middle	36	5	0



Correlation of vitamin-D status and socioeconomic status among controls:

71% of women with optimal levels of vitamin-D among the control groups were in the middle socioeconomic category.

Socioeconomic status	vitamin d levels among controls	
	optimal	Mild moderate
Lower	15	13
Middle	38 P value=0.012	9

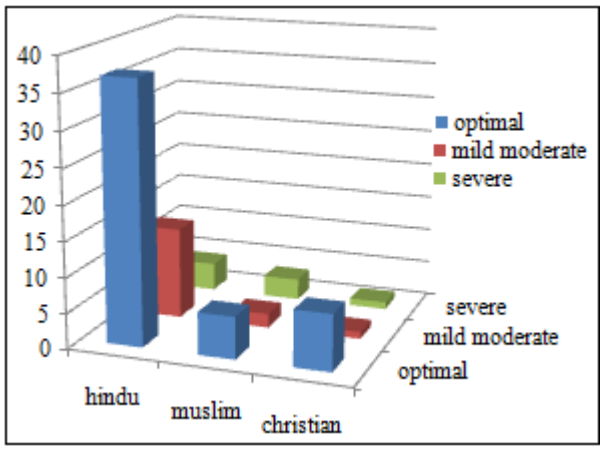


Socioeconomic status in correlation with vitamin-D was found to be statistically significant with a p value of 0.012.

Religion and its effects on gdm due to vitamin d status:

Women with gestational diabetes mellitus were classified based on the religions to study the effect of social customs:

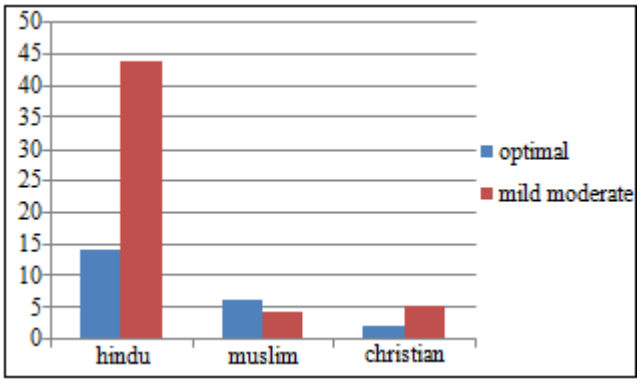
Religion	GDM cases		
	optimal	Mild-moderate	Severe
Hindu (54)	37	13	4
Muslim (11)	6	2	3
Christian (10)	8	1	1



Since majority of women with gestational diabetes mellitus belonged to the hindu category, groups were not comparable in regards to vitamin-D status.

Religion and its effects on controls

Religion	vitamin –D levels among controls	
	optimal	Mild-moderate
Hindu (58)	14	44
Muslim (10)	6	4
Christian (7)	2	5



Women who were included in the study belonged to different religions and were found to be distributed unequally and hence vitamin –D status or gestational diabetes mellitus could not be

Secondary Outcomes and Its Effect on GDM

Category	Cases (GDM)
Diet	Significant- Vegetarian Diet
Sunlight Exposure	Significant <=15-30 Minutes of Exposure
Socioeconomic Status	Significant-Lower Socioeconomic Status
Skin Colour	Significant Dark Brown
Religion	Not Significant

6. Discussion

In the current study, the results show a statistically significant inverse relationship between mid-trimester maternal vitamin–D levels and gestational diabetes mellitus. In a study population of 150, 10.7% of women with gestational diabetes mellitus were found to have severe vitamin-D deficiency. Hence there is an increasing odds of developing gestational diabetes mellitus amongst women with low second trimester vitamin-D levels.

Secondary outcomes associated with Vitamin-D deficiency among cases and controls need to be considered for prevention. Diet has a major influence in causing vitamin deficiency. Changing food habits, low dietary intake may be responsible in causing the deficiency state. In our study 62% of severe vitamin–D deficiency was noted in women consuming vegetarian diet, and an associated confounding factor could be low socioeconomic status (100% of cases belonging to severe category of vitamin-D deficiency).The vegetarian diet consumed largely by women under study had a lower RDA of vitamin–D compared to women who consumed non vegetarian diet like fish (mackerel, salmon) which are better sources of vitamin-D.

The vitamin D-deficiency during pregnancy is caused by a lack of adequate sunlight exposure at the appropriate time, needed to synthesize vitamin D3 in the skin, coupled with overall intake that are too low to meet the increased demands of pregnancy.

In our study we found that 75% of women belonging to severe vitamin-D deficiency had 15 minutes of exposure to sunlight in the mid-day time particularly between 10 am to 3 am.

Even though living in a tropical latitude, additional contributory aspects like high amount of atmospheric pollution, ‘purdah’ system, dark pigmented skin, humidity, lesser physical activity could lead to a deficiency status.

In our study, women with dark brown pigmented skin compared to moderate brown pigmented skin showed severe vitamin-D deficiency. Increase in the melanin content prevents UV-B radiations and hence prevents effective absorption of vitamin-D.
In India, various religions have its own diverse social customs and cultural traditions like the “purdah” system , “burqa” to fully covered clothes which might have a confounding effect in causing a vitamin-D deficiency status. We did not find a statistical significance among our cases and controls group.

In Zhang et tal, (7) United states Washington, 2008 study,which was a nested case- control study of 57 cases of GDM, maternal 25 (OH)D levels at measured at 16 weeks’ gestation were 20% lower among women who later developed GDM. Severity of vitamin-D deficiency was not taken part of the study. In a study done by Clifton-bligh et al (8) in Australia, 2008, 32% of women with gestational diabetes mellitus were found to have vitamin –D levels less than 10 ng/ml. 25 (OH)D levels were significantly lower than among women without gestational diabetes. In soheiyal et tal (9) study, Iran 2011, 65 women with gestational diabetes mellitus were studied; 83% of women with gestational diabetes mellitus had 25 (OH)d<50 ng/dl vs 71% of controls. This study did not classify the vitamin-D deficiency as mild or moderate category. In a study done by Makgoba et al (10), Iran-2011, 741 women were studied, 29 % of participants had 25 (OH)D levels <15 ng/dL. Their study concluded that Gestational diabetes mellitus was associated with participants with <15 ng/dl than with those who had >25 ng/dl. Socioeconomic demographics were not considered. H. Burris et al (11) ,Harvard public health -

2014,studied 1087 women,13.2% of women who had vitamin-D less than 15 ng/dl developed gestational diabetes mellitusA initial screening glucose challenge test was used and same sample was being used to test the levels of vitamin-D, as the glucose intolerance in regards to formal diagnosis of a Gestational diabetes mellitus predates the sample drawn, physiological changes associated with hyperglycemia lowering vitamin-D values could not be prevented.

In our study, we found an inverse relationship between vitamin-D and gestational diabetes mellitus in consistent with other studies. Our study has several strengths including a healthy population, the ability to account for dietary factors and physical activity and history pertaining to sunlight exposure.

Adjustment for self-reported dietary intake of eggs, milk and fish ,physical activity, skin pigmentation did not materially change the higher odds of GDM among women with 25 (OH)D levels less than 10 vs. ≥25 nmol/L suggesting vitamin D has an independent association with glucose tolerance from foods and nutrients with which it tracks closely. Major drawbacks of the study were smaller sample size, expensive Vitamin-d kits, Pregestational Body mass Index notbeing considered to study further associated confounding factors like obesity.

Our study raises the possibility that high risk women who are tested with Vitamin-D levels may benefit from supplementation and that such an intervention might decease their risk of GDM. Randomized controlled trials are needed to confirm this assertion.

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