Nutrición Hospitalaria

Asociaciones entre los niveles de vitamina D y los marcadores de glucosa en mujeres embarazadas y sus bebés en Puerto Rico

Associations between vitamin D levels and glucose metabolism markers among pregnant women and their infants in Puerto Rico

10.20960/nh.03600

11/29/2021

OR 3600

Associations between vitamin D levels and glucose metabolism markers among pregnant women and their infants in Puerto Rico

Asociaciones entre los niveles de vitamina D y los marcadores de glucosa en mujeres embarazadas y sus bebés en Puerto Rico

Cristina Palacios[1], Maria Angelica Trak-Fellermeier[1], Marytere Melendez[2], Maribel Campos[3], Jeremy Pomeroy[4], Kai Guo[2], Paul W. Franks[5], and Kaumudi Joshipura[2]

[1]Department of Dietetics and Nutrition. Robert Stempel College of Public Health & Social Work. Florida International University. Miami, Florida. USA. [2]Center for Clinical Research and Health Promotion. Medical Sciences Campus. University of Puerto Rico. San Juan, Puerto Rico. [3]Center for Community Outreach for Health Across the Lifespan, Dental and Craniofacial Genomics Core. Medical Sciences Campus. University of Puerto Rico. San Juan, Puerto Rico. [4]Center for Clinical Epidemiology and Population Health. Marshfield Clinic Research Foundation. Marshfield Clinic Health System. Marshfield, Wisconsin. USA. [5]Genetic and Molecular Epidemiology Unit. Department of Clinical Sciences. Lunds Universitet. Skånes Universitetssjukhus i Malmö. Malmö, Sweden

Received: 01/03/2021
Accepted: 03/09/2021

Correspondence: Cristina Palacios. Department of Dietetics and Nutrition. Robert Stempel College of Public Health & Social Work. Florida International University. AHC5, 11200 SW 8th St #500. Miami, Florida 33199. USA
e-mail: cristina.palacios@fiu.edu

Contributorship statement: CP, MC, JP, PWF, and KJ designed and prepared the study concept. CP and KG analyzed the data. CP drafted the manuscript with advice from MATF and KJ. MM, MC, JP, and PWF were involved in the critical revision of the manuscript. All authors read and approved the final manuscript.

Competing interests: none.

Funding: LIFE-Moms is supported by the National Institutes of Health through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, U01 DK094418, U01 DK094463, U01 DK094416, 5U01 DK094466 (RCU), the National Heart, Lung, and Blood Institute (NHLBI, U01 HL114344, U01 HL114377), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD, U01 HD072834), the National Center for Complementary and Integrative Health (NCCIH), the NIH Office of Research in Women's Health (ORWH), the Office of Behavioral and Social Science Research (OBSSR), the Indian Health Service, and the Intramural Research Program of the NIDDK. The PEARLS study was conducted at the PRCTRC (Puerto Rico Clinical and Translational Research Consortium) funded by the National Institute on Minority Health and Health Disparities of the National Institutes of Health under award number 8U54MD007587-03.

Acknowledgements: the authors acknowledge the valuable contribution of Keimari Mendez, MD, Lizzie Ramos, MD, Juana Rivera, Vivian Rivera, Elaine Rodríguez, and José Luis Vergara, and of the Research Assistants who participated in the recruitment, assessment, intervention, and retention efforts during the study. The authors specially thank the PEARLS study participants.

ABSTRACT

Objectives: low vitamin D during pregnancy is common and could adversely affect health outcomes. This study evaluated vitamin D status during pregnancy and early in life, and its association with glucose metabolism.

Methods: maternal serum 25(OH)D, glucose, and insulin levels were measured longitudinally during pregnancy in Hispanic women with overweight/obesity (n = 31) and their infants at birth and 4 months.

Results: insulin and HOMA-IR levels were higher among women with vitamin D below adequate levels compared to those with adequate levels in pregnancy ($p < 0.05$). Late in pregnancy, as vitamin D increased by one unit (ng/mL), insulin decreased by 0.44 units and HOMA-IR by 0.09 units. Maternal vitamin D late in pregnancy was correlated with infant vitamin D levels at birth ($r = 0.89$; $p < 0.01$) and 4 months ($r = 0.9$; $p = 0.04$), and with glucose ($r = 0.79$; $p = 0.03$) and insulin ($r = 0.83$; $p = 0.04$) at 4 months.

Conclusion: maternal vitamin D status was associated with maternal and infant glucose metabolism in this sample.

Keywords: Vitamin D. Pregnancy. Infant. Glucose. Insulin.

RESUMEN

Objetivos: un bajo nivel de vitamina D durante el embarazo es común y puede tener consecuencias adversas en la salud. Este estudio evaluó el nivel de vitamina D en mujeres embarazadas y sus bebés, así como su asociación con los marcadores de glucosa.

Métodos: los niveles séricos de 25(OH)D, glucosa e insulina se midieron longitudinalmente en mujeres embarazadas hispanoamericanas con sobrepeso/obesidad (n = 31) y en sus bebés, desde el nacimiento hasta los 4 meses de edad, en Puerto Rico.

Resultados: los niveles maternos de insulina y HOMA-IR eran mayores en las mujeres con niveles de vitamina D por debajo de lo considerado adecuado, comparado con aquellas con niveles adecuados durante todo el embarazo ($p < 0,05$). Al final del embarazo, a medida que los niveles de vitamina D aumentaron, por cada unidad (ng/mL) de aumento, la insulina disminuyo en 0,44 unidades y el HOMA-IR en 0,09 unidades. El nivel de vitamina D al final del embarazo se correlacionó con los niveles del bebé al nacer ($r = 0,89$; $p < 0,01$) y a los 4 meses ($r = 0,9$; $p = 0,04$), y con los niveles de glucosa ($r = 0,79$; $p = 0,03$) e insulina ($r = 0,83$; $p = 0,04$) a los 4 meses.

Conclusión: el nivel materno de vitamina D se asoció con los marcadores maternos e infantiles de glucosa en esta muestra.

Palabras clave: Vitamina D. Embarazo. Lactante. Glucosa. Insulina.

INTRODUCTION

Adequate maternal vitamin D status during pregnancy is linked with maternal health outcomes (1). Serum 25-hydroxyvitamin D (25(OH)D) levels increase initially during pregnancy, peaking towards the end of pregnancy (2). This increase is important for maintaining high levels of the active form of vitamin D ($1,25(OH)_2D$) from early in pregnancy until delivery (3). Although this large increase in $1,25(OH)_2D$ is dependent on 25(OH) serum D levels, it is independent of calcium metabolism, a unique feature of pregnancy for maintaining $1,25(OH)_2D$ at high levels (4). The enzyme 1-alpha-hydroxylase, which is responsible for the hydroxylation of 25(OH)D into the active form of vitamin D in maternal kidneys, is also expressed by the maternal decidual and fetal placenta (5). Also, vitamin D receptors are present in the placenta; therefore, $1,25(OH)_2D$ is also synthesized locally by the placenta (5). The fetus

completely relies on the vitamin D supply of the mother, and vitamin D, through the modulation of the vitamin D receptor, has been shown to be crucial during fetal development, such as implantation, placental vascularization and metabolism, modulation of immune function, and neurological development (6). In addition, vitamin D promotes cellular differentiation, apoptosis, and fetal skeletal growth, and may be involved in fetal programming (5). These actions highlight the importance of vitamin D on pregnancy and on fetal development.

An important action of vitamin D during pregnancy is the regulation of glucose. Specifically, vitamin D modulates vitamin D receptors in pancreatic beta cells, which in turn affect insulin secretion (7). With vitamin D deficiency, vitamin D receptors may not be activated or indirect actions of calcemic hormones could take place, all of which could lead to variations in insulin secretion and glucose intolerance (8). This role of vitamin D may explain why vitamin D deficiency increases the risk of gestational diabetes (9,10). In addition, obesity can worsen this process, as it has been shown that low vitamin D status is inversely associated with obesity (11). Furthermore, it has been shown that vitamin D has direct effects on the regulation of the insulin receptor gene, which could also affect insulin resistance (12). However, there are limited studies prospectively examining how circulating 25(OH)D, early and late in pregnancy, affects glucose homeostasis. Most studies have associated maternal vitamin D status early in pregnancy with adverse outcomes later in pregnancy (13-15), or have assessed both vitamin D status and health outcomes at mid or at the end of pregnancy (16-21). Also, several studies have evaluated changes in vitamin D status throughout pregnancy (2,22-26). However, to our knowledge, only four studies have evaluated the longitudinal associations between vitamin D status and glucose homeostasis among Brazilian (23), Iranian (24), Irish (25), and Swedish (27) pregnant women, with mixed results. No study has evaluated this association among Hispanics, a group with the

highest risk of diabetes in the US (28), also with a high risk of low vitamin D status (29). Also, to our knowledge, only one study has evaluated the association between maternal vitamin D status and infant glucose homeostasis at birth and in early life (18).

This pilot study prospectively assessed vitamin D status in Hispanic women with overweight/obesity early in pregnancy and at the end of pregnancy, and its association with changes in glucose markers. This study also evaluated the modulation of maternal vitamin D status on infant glucose homeostasis during the first months of life.

METHODS

Overall design

This is a secondary analysis of data from the PEARLS study (Pregnancy and EARly Lifestyle Improvement Study), a lifestyle intervention focused on improving physical activity and diet quality, and optimizing caloric intake (30,31). PEARLS was approved by the University of Puerto Rico Institutional Review Board and by the LIFE-Moms Data and Safety Monitoring Board. Participants provided their written informed consent.

We evaluated changes in maternal vitamin D status from early to late pregnancy, and its association with glucose homeostasis in mothers (30,31). Specifically, we evaluated changes in maternal serum 25(OH)D from before or at the 16th week of gestation to the end of pregnancy (35-37 weeks of gestation), and its association with changes in fasting glucose and insulin between the 16th week or before and 35-37 weeks' gestation. We also assessed the relationship between 25(OH)D levels in infants and its association with fasting glucose and insulin levels at 16-24 weeks of life.

Sample

Participants were pregnant women seeking prenatal care at the University Hospital and attending WIC offices. Inclusion criteria were 18 years or older, singleton, identified with overweight or obesity, $\leq$ 16 weeks of pregnancy/gestational age, without contraindications for aerobic exercise, and generally healthy (not diabetes, anemia, HIV, hypertension, seizure disorder, hyperthyroidism, heart disease, among others). More details have been published elsewhere (30).

Vitamin D status

Serum 25(OH)D levels were assessed from fasting blood samples in pregnant women at or before week 16 and at weeks 35-37 of gestation. A 5-mL blood sample was collected by venipuncture by a trained phlebotomist. For infants, an 18-mL blood sample was collected by venipuncture by a trained phlebotomist at 16-24 weeks of age. Serum separator tubes were used, and serum 25(OH)D levels were measured using a commercially available direct competitive chemiluminescence immunoassay (Liaison, DiaSorin S.p.A., Saluggia, VC, Italy). Vitamin D levels were categorized as deficient if levels were ≤ 12 ng/mL, inadequate if levels were 12-19 ng/mL, and adequate if levels were ≥ 20 ng/mL, as suggested by the Institute of Medicine criteria for bone health (32). We added the category of optimal if levels were ≥ 30 ng/mL, as suggested by the Endocrine Society for optimal health (33). Samples were collected all year round.

Glucose biomarkers

Fasting glucose, insulin, and HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) were also assessed at the same time points. Morning fasting blood samples were drawn using a standard protocol and silicone-coated sterile vacutainer blood collection tubes. Serum glucose levels in a minimum volume of 200 μL were measured using an enzymatic colorimetric assay. The coefficient of variation (CV) within the

laboratory was 1.7 %. An aliquot of approximately 2 mL was sent to a reference laboratory within four hours to measure serum insulin levels using an immunoenzymometric assay. The intra- and inter-assay CVs for the measurement of insulin were 1.49 % and 4.42 %, respectively. HOMA-IR was calculated as insulin levels x glucose / 405.

Anthropometric measurements

Pre-pregnancy body mass index was calculated from a self-reported questionnaire. Weight was assessed before 16 weeks of gestation and at 35-37 weeks by trained research personnel using a digital scale (BWB-100P, TANITA Corp., Illinois, USA), and height was assessed using a wall-mounted stadiometer (Seca® 222, Hamburg, Germany). Infant birth weight and birth length were assessed by trained research personnel within 7 days of birth and again at 16-24 weeks of delivery using a digital scale (Seca® 354, Hamburg, Germany), and an infantometer (Ellard Instrumentation Ltd., Monroe, Washington, USA), respectively.

Socio-demographics and health

The following socio-demographic variables were self-reported by participants using a questionnaire: age, race/ethnicity, education, medical history, family income, gestational age, parity, BMI status early in pregnancy, and prior gestational diabetes.

Patient and public involvement

Patients and the public were not involved in this study.

Statistical analysis

Descriptive statistics included mean and standard deviations for continuous variables, and frequency and proportion tables for categorical variables. Chi-square and Fisher’s exact tests were used to compare differences in categorical variables, and paired t-test and

paired samples Wilcoxon's test were used to compare differences in continuous variables from early in pregnancy to end of pregnancy. In addition to p-values, 95 % confidence intervals (CI) were also provided. Spearman's correlation coefficients were used to evaluate the association between maternal vitamin D levels from early to late pregnancy with maternal and infant glucose metabolism biomarkers and with infant vitamin D levels at birth and 4 months of age. Under the circumstance of very small samples, we either used the method from Goodman (34) to standardize the p-value, or used the formula from Perez and Pericchi (35) to adapt the alpha significance value in all analyses. Independent two-sample t-test and one-way ANOVA analyses were used to compare glucose biomarkers and insulin levels by vitamin D status (below adequate or adequate). Simple and multiple linear regression analyses were used to model and quantify the strength of the relationships between glucose, insulin, and HOMA-IR levels and vitamin D levels. We also standardized the dependent variables such that we could easily interpret the standardized beta coefficient as the effect of a change of one unit of the independent variable on the standard deviation of dependent variables. A bootstrap approach was employed for paired t-tests and linear regression analyses to compute the bootstrapped biases, standard errors, and confidence intervals. McNemar-Bowker tests were used to test the independence of paired nominal variables, such as maternal vitamin D status early in pregnancy and at the end of pregnancy.

RESULTS

A total of 31 pregnant women were recruited in the study. All were Hispanic, with a gestational age ≤ 16 weeks, participants in the WIC program, and presented overweight (26 %) or obesity (74 %) (Table I). A total of 51.6 % had college education, 80.6 % had an annual income < $ 20,000, 71 % had other children, and only 5.4 % had prior gestational

diabetes. At baseline, only 45 % were taking their prenatal supplements and none were taking vitamin D supplements.

Figure 1 shows vitamin D status early in pregnancy and at the end of pregnancy. Most women had adequate vitamin D status, with none classified as deficient, as defined by the IOM. However, using the Endocrine Society cut-off levels, only 22.6 % of women at the beginning and 16.7 % at the end of pregnancy had optimal levels ($p > 0.05$). Figure 2 shows individual change in serum 25(OH)D from early to end of pregnancy. There was a large variability in this change. However, mean changes in serum 25(OH)D levels were not significant between early (25.2 ± 5.8 ng/mL) and late pregnancy (24.8 ± 6.1 ng/mL; $p > 0.05$; 95 % CI, -2.38, 3.53). Use of prenatal supplements early in pregnancy was negatively associated with vitamin D status early in pregnancy ($Chi^2 = 7.50$; $p = 0.02$) but use of prenatal supplements late in pregnancy was not associated with vitamin D status late in pregnancy (data not shown). Among those with optimal or adequate levels early in pregnancy ($n = 26$), only 35 % were using any dietary supplements while all participants with inadequate levels ($n = 5$) were using supplements early in pregnancy. At the end of pregnancy, 46 % of those with optimal or adequate levels were using any dietary supplements, while only 20 % of those with inadequate levels were using supplements. The use of supplements early in pregnancy was significantly associated with change in vitamin D status during pregnancy ($Chi^2 = 8.33$; $p = 0.04$). However, weight status early in pregnancy was not associated with gestational changes in vitamin D status ($Chi^2 = 2.50$; $p = 0.48$).

With respect to maternal glucose, insulin or HOMA levels, we detected a significant decrease in glucose levels from early in pregnancy to late pregnancy (Fig. 3); this was not influenced by vitamin D status. However, regardless of time in pregnancy, insulin levels among pregnant women with vitamin D below adequate levels were higher than among those with adequate vitamin D status ($p < 0.05$) from one-way ANOVA

analyses (Fig. 4). Late in pregnancy, as the vitamin D level increased by one unit, the insulin level decreased by 0.44 units. Similar results were found with HOMA early in pregnancy ($p = 0.04$ for one-way ANOVA; $p < 0.001$ and 95 % CI, -2.18, -0.72 for independent two samples t-test); as the vitamin D level increased by one unit, the HOMA level decreased by 0.09 units late in pregnancy.

Infant vitamin D status at birth and at 4 months of age is shown in figure 5. At birth, 40 % had optimal levels but also 40 % had inadequate levels. At 4 months of age, most had optimal levels (60 %); however, 10 % were deficient; there were no significant differences between vitamin D levels at birth and 4 months of age ($p = 0.88$, 95 % CI (-12.0, 13.8)). Infant vitamin D levels at birth ($r = 0.68$, $n = 6$, $p = 0.04$) and at 4 months ($r = 0.64$, $n = 10$, $p = 0.02$) were significantly correlated with maternal vitamin D level early in pregnancy. For every unit that maternal vitamin D levels increased early in pregnancy, infant vitamin D levels increased by 2.13 units (with a standardized beta coefficient of 0.18) at birth and by 0.93 units (with a standardized beta coefficient value of 0.11) at 4 months. We also observed that maternal vitamin D levels early in pregnancy were significantly correlated with infant insulin levels at 4 months ($r = 0.65$, $n = 11$, $p = 0.01$); for every unit that maternal vitamin D levels increased early in pregnancy, infant insulin levels at 4 months also increased by 1.04 units of ng/mL (with a standardized beta coefficient value of 0.15). Maternal vitamin D level in late pregnancy was also significantly correlated to the infants' vitamin D level at birth ($r = 0.89$, $n = 6$, $p < 0.01$), with every 1 unit increase in maternal vitamin D levels late in pregnancy increasing the infants' vitamin D levels by 1.31 units with a standardized beta coefficient value of 1.11. In addition, maternal vitamin D, both levels and status, in late pregnancy were significantly correlated to infant vitamin D ($r = 0.9$, $n = 5$, $p < 0.01$; one-way ANOVA $p = 0.04$), glucose ($r = 0.79$, $n = 7$, $p < 0.01$; one-way ANOVA $p = 0.03$) and insulin ($r = 0.83$, $n = 6$, $p < 0.01$; one-way ANOVA

p = 0.04) levels at 4 months. A 1 unit increase in maternal vitamin D level on average was associated with an infant's vitamin D levels increase by 0.93 units (with a standardized beta coefficient value of 0.11) and the infant’s glucose levels increased by 1.98 units (with a standardized beta coefficient value of 0.13).

DISCUSSION

In this pilot study, among a group of low-income Hispanic pregnant women with overweight/obesity we observed a large variability in maternal serum 25(OH)D level changes from early in pregnancy to end of pregnancy, but in general there was no peak in these levels towards the end of pregnancy. Maternal serum 25(OH)D levels early in pregnancy were inversely correlated with maternal HOMA levels at the end of pregnancy. Also, maternal serum 25(OH)D levels at end of pregnancy were inversely correlated with maternal insulin levels at the end of pregnancy, with infant serum 25(OH)D levels at birth and with infant glucose at 4 months of age.

We did not observe any peak in serum 25(OH)D levels towards the end of pregnancy, as reported by others (2,22,27,36). The study among Danish pregnant women found that serum 25(OH)D levels increased from week 18 to week 32, and then slightly decreased (22). However, the study among Irish (25) and Iranian (24) pregnant women did not observe this peak, and actually reported a small decrease in maternal serum 25(OH)D levels from early to mid or end of pregnancy. Similarly, a study among 30 Irish pregnant women, and another study among 40 Belgian pregnant women consistently found that serum 25(OH)D levels decreased from weeks 15-18 to weeks 28-32, and further decreased during weeks 36-40 of pregnancy (26,37). This decrease may be related to blood dilution towards the third trimester but also to other factors, such as use of prenatal supplements. Prenatal supplements usually contain 400 IU of vitamin D per tablet, which may not be enough to

maintain an adequate vitamin D status in pregnancy. In fact, in our study, the use of prenatal vitamins was negatively associated with vitamin D status early in pregnancy, but this association was not seen at the end of the study. Similarly, in a study among Swedish pregnant women, the use of prenatal supplements was only associated with vitamin D status early in pregnancy, but not at the end of pregnancy (2). However, among pregnant women from the UK, the use of prenatal supplements was associated with vitamin D status during the first, second, and third trimester (38). The large variability in vitamin D changes in pregnancy between studies could also be explained by several other factors that influence vitamin D status, such as age, body weight, skin pigmentation, sun exposure, use of sunscreen, clothing, season, and latitude (33), among others. Although many studies controlled for season when evaluating changes in serum 25(OH)D levels (2,14,18,36), other factors were usually not taken into account.

From early in pregnancy, there is an increase in maternal fat stores and an initial increase in insulin levels to prepare for the needs of the growing fetus later in pregnancy (39). Late in pregnancy, there is a decrease in insulin sensitivity and a corresponding increase in insulin resistance, which results in an increase in maternal glucose levels to provide enough substrate to meet the large needs of the growing fetus. The placenta contributes to these endocrine adaptations, particularly during the mid and late pregnancy stages, and thus pregnancy has been described as a mild diabetogenic state (40). These processes may be modulated during pregnancy by active vitamin D through its actions on pancreatic beta cells (7) and on the regulation of the insulin receptor gene (12). However, in the present study, we did not observe an increase in insulin or glucose levels over pregnancy, and we found that maternal serum 25(OH)D levels early in pregnancy were inversely correlated with maternal HOMA levels at the end of pregnancy, and that maternal serum 25(OH)D levels at the end of pregnancy were inversely

correlated with maternal insulin levels at the end of pregnancy. The longitudinal study among Iranian women found that serum 25(OH)D levels were inversely associated with HbA1c at the beginning of pregnancy, and serum 25(OH)D levels in the second trimester were inversely associated with fasting insulin and glucose levels at that same time point (24). In the Swedish women, maternal serum 25(OH)D levels were inversely associated with blood glucose early in pregnancy and with blood glucose trajectory during pregnancy, but insulin was not measured (27). The study among Irish women found that low serum 25(OH)D levels early in pregnancy were significantly associated with higher plasma glucose later in pregnancy, independently of season (25). However, it was not related to insulin resistance after controlling for season and other confounders. In Brazilian women, those with low vitamin D status early in pregnancy had higher fasting glucose levels compared to women with vitamin D sufficiency, and a smaller increase in insulin (23).

To our knowledge, no study has associated maternal serum 25(OH)D levels at the end of pregnancy with infant insulin and glucose levels at birth (from samples not taken from cord blood) and at 4 months of age. In the present study, we showed a direct correlation between maternal serum 25(OH)D levels at the end of pregnancy with infant serum 25(OH)D levels at birth, and with infant glucose at 4 months of age ($p < 0.05$). This could be explained by the long-lasting actions of vitamin D during pregnancy on fetal programming (5). These long-lasting effects have important implications for infant health during the first months of life, as infants rely completely on the vitamin D stores acquired in utero (4). However, more studies are needed to understand how maternal vitamin D status could impact glucose homeostasis in the neonate and later in life. One strength of this study is that it includes a homogenous group of Hispanic women with overweight/obesity during pregnancy. Also, it evaluated serum 25(OH)D levels and glucose homeostasis

biomarkers at different times in pregnancy (first and last trimester), and in infants at birth and 4 months later. An important limitation was the small sample size and missing data for infant measures, which did not allow to adjust the analysis for potential confounders.

In conclusion, the present study showed that maternal vitamin D status was associated with maternal HOMA and insulin levels among low-income, Hispanic women with overweight/obesity during pregnancy. Also, maternal vitamin D status at the end of pregnancy was associated with neonatal serum 25(OH)D levels and with infant glucose homeostasis at 4 months of age. Well-designed observational and interventional studies are needed to determine the role of vitamin D on gestational and infant glucose metabolism. This may be particularly important among groups at high risk of diabetes.

REFERENCES

1. Palacios C, De-Regil LM, Lombardo LK, Peña-Rosas JP. Vitamin D supplementation during pregnancy: Updated meta-analysis on maternal outcomes. J Steroid Biochem Mol Biol [Internet] 2016 [cited 2017 Mar 2];164:148-55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26877200. DOI: 10.1016/j.jsbmb.2016.02.008
2. Lundqvist A, Sandström H, Stenlund H, Johansson I, Hultdin J. Vitamin D Status during Pregnancy: A Longitudinal Study in Swedish Women from Early Pregnancy to Seven Months Postpartum. Slominski AT, editor. PLoS One [Internet] 2016 [cited 2017 Mar 2];11:e0150385. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26938997. DOI: 10.1371/journal.pone.0150385
3. Møller UK, Streym S, Heickendorff L, Mosekilde L, Rejnmark L.

Effects of 25OHD concentrations on chances of pregnancy and pregnancy outcomes: a cohort study in healthy Danish women. Eur J Clin Nutr [Internet] 2012 [cited 2017 Mar 2];66:862-8. Available from: http://www.nature.com/doifinder/10.1038/ejcn.2012.18. DOI: 10.1038/ejcn.2012.18

4. Mulligan ML, Felton SK, Riek AE, Bernal-Mizrachi C. Implications of vitamin D deficiency in pregnancy and lactation. Am J Obstet Gynecol [Internet] 2010 [cited 2017 Mar 2];202:429.e1-9. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0002937809010035. DOI: 10.1016/j.ajog.2009.09.002
5. Liu NQ, Hewison M. Vitamin D, the placenta and pregnancy. Arch Biochem Biophys [Internet] 2012 [cited 2019 Jan 24];523:37-47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22155151. DOI: 10.1016/j.abb.2011.11.018
6. Gernand AD, Schulze KJ, Stewart CP, West KP, Christian P. Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. Nat Rev Endocrinol [Internet] 2016 [cited 2019 Jan 24];12:274-89. Available from: http://www.nature.com/articles/nrendo.2016.37. DOI: 10.1038/nrendo.2016.37
7. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 2007;92(6):2017-29. DOI: 10.1210/jc.2007-0298
8. Chagas CE, Borges MC, Martini LA, Rogero MM. Focus on vitamin D, inflammation and type 2 diabetes. Nutrients 2012;4:52-67. DOI: 10.3390/nu4010052
9. Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review

and meta-analysis of observational studies. BMJ [Internet] 2013 [cited 2017 Mar 2];346:f1169. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23533188. DOI: 10.1136/bmj.f1169

10. Zhang M-X, Pan G-T, Guo J-F, Li B-Y, Qin L-Q, Zhang Z-L. Vitamin D Deficiency Increases the Risk of Gestational Diabetes Mellitus: A Meta-Analysis of Observational Studies. Nutrients [Internet] 2015 [cited 2019 Jan 31];7:8366-75. Available from: http://www.mdpi.com/2072-6643/7/10/5398. DOI: 10.3390/nu7105398
11. Vimaleswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, et al. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. PLoS Med 2013;10:e1001383.
12. Maestro B, Molero S, Bajo S, Davila N, Calle C. Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D(3). Cell Biochem Funct 2002;20:227-32. DOI: 10.1002/cbf.951
13. Lacroix M, Battista M-C, Doyon M, Houde G, Ménard J, Ardilouze J-L, et al. Lower vitamin D levels at first trimester are associated with higher risk of developing gestational diabetes mellitus. Acta Diabetol [Internet] 2014 [cited 2019 Jan 24];51:609-16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24526261. DOI: 10.1007/s00592-014-0564-4
14. Hauta-alus HH, Viljakainen HT, Holmlund-Suila EM, Enlund-Cerullo M, Rosendahl J, Valkama SM, et al. Maternal vitamin D status, gestational diabetes and infant birth size. BMC Pregnancy Childbirth [Internet] 2017 [cited 2019 Jan 28];17:420. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29246128. DOI: 10.1186/s12884-017-1600-5

15. Rodriguez A, García-Esteban R, Basterretxea M, Lertxundi A, Rodríguez-Bernal C, Iñiguez C, et al. Associations of maternal circulating 25-hydroxyvitamin D3 concentration with pregnancy and birth outcomes. BJOG An Int J Obstet Gynaecol [Internet] 2015 [cited 2019 Jan 29];122:1695-704. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25208685. DOI: 10.1111/1471-0528.13074
16. El Lithy A, Abdella RM, El-Faissal YM, Sayed AM, Samie RMA. The relationship between low maternal serum vitamin D levels and glycemic control in gestational diabetes assessed by HbA1c levels: an observational cross-sectional study. BMC Pregnancy Childbirth [Internet] 2014 [cited 2019 Jan 24];14:362. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25308347. DOI: 10.1186/1471-2393-14-362
17. Kramer CK, Swaminathan B, Hanley AJ, Connelly PW, Sermer M, Zinman B, et al. Vitamin D and Parathyroid Hormone Status in Pregnancy: Effect on Insulin Sensitivity, β-cell Function, and Gestational Diabetes Mellitus. J Clin Endocrinol Metab [Internet] 2014 [cited 2019 Jan 24];99:4506-13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25202819. DOI: 10.1210/jc.2014-2341
18. Casey C, McGinty A, Holmes VA, Patterson CC, Young IS, McCance DR. Maternal vitamin D and neonatal anthropometrics and markers of neonatal glycaemia: Belfast Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. Br J Nutr [Internet] 2018 [cited 2019 Jan 28];120:74-80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29936925. DOI: 10.1017/S0007114518001320
19. Mutlu N, Esra H, Begum A, Fatma D, Arzu Y, Yalcin H, et al. Relation of maternal vitamin D status with gestational diabetes mellitus and perinatal outcome. Afr Health Sci [Internet] 2015

[cited 2019 Jan 29];15:523-31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26124799. DOI: 10.4314/ahs.v15i2.27

20. Gernand AD, Simhan HN, Klebanoff MA, Bodnar LM. Maternal serum 25-hydroxyvitamin D and measures of newborn and placental weight in a U.S. multicenter cohort study. J Clin Endocrinol Metab [Internet] 2013 [cited 2019 Jan 29];98:398-404. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23162094. DOI: 10.1210/jc.2012-3275
21. Josefson JL, Reisetter A, Scholtens DM, Price HE, Metzger BE, Langman CB, et al. Maternal BMI Associations with Maternal and Cord Blood Vitamin D Levels in a North American Subset of Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Participants. Nerurkar P V., editor. PLoS One [Internet] 2016 [cited 2019 Jan 31];11:e0150221. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26942930. DOI: 10.1371/journal.pone.0150221
22. Milman N, Hvas A-M, Bergholt T. Vitamin D status during normal pregnancy and postpartum. A longitudinal study in 141 Danish women. J Perinat Med [Internet] 2011 [cited 2019 Jan 29];40:57-61. Available from: https://www.degruyter.com/view/j/jpme.2012.40.issue-1/jpm.2011.120/jpm.2011.120.xml. DOI: 10.1515/JPM.2011.120
23. Benaim C, Cocate PG, de Barros EG, Alves-Santos NH, Figueiredo ACC, Franco-Sena AB, et al. Longitudinal association of 25-hydroxyvitamin D with adipokines and markers of glucose metabolism among Brazilian pregnant women. Br J Nutr [Internet] 2019 [cited 2019 Feb 1];121:42-54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30588902. DOI: 10.1017/S0007114518003057
24. Jafarzadeh L, Motamedi A, Behradmanesh M, Hashemi R. A

Comparison of Serum Levels of 25-hydroxy Vitamin D in Pregnant Women at Risk for Gestational Diabetes Mellitus and Women Without Risk Factors. Mater Socio Medica [Internet] 2015 [cited 2019 Jan 24];27:318. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26622198. DOI: 10.5455/msm.2015.27.318-322

25. O'Brien EC, O'Sullivan EJ, Kilbane MT, Geraghty AA, McKenna MJ, McAuliffe FM. Season and vitamin D status are independently associated with glucose homeostasis in pregnancy. Nutr Metab (Lond) [Internet] 2017 [cited 2019 Jan 24];14:50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28775759. DOI: 10.1186/s12986-017-0203-5

26. Zhang JY, Lucey AJ, Horgan R, Kenny LC, Kiely M. Impact of pregnancy on vitamin D status: a longitudinal study. Br J Nutr [Internet] 2014 [cited 2019 Jan 31];112:1081-7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25159824. DOI: 10.1017/S0007114514001883

27. Walsh M, Bärebring L, Augustin H. Avoiding maternal vitamin D deficiency may lower blood glucose in pregnancy. J Steroid Biochem Mol Biol [Internet] 2019 [cited 2019 Jan 24];186:117-21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30308320. DOI: 10.1016/j.jsbmb.2018.10.003

28. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. JAMA [Internet] 2015 [cited 2017 Aug 3];314:1021. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26348752. DOI: 10.1001/jama.2015.10029

29. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol [Internet] 2013;1-8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24239505.

30. Trak-Fellermeier MA, Campos M, Meléndez M, Pomeroy J, Palacios C, Rivera-Viñas J, et al. The Pregnancy and EARLy Lifestyle Improvement Study: Maternal and neonatal anthropometric outcomes. A Randomized Clinical Trial. BMC Pregnancy Childbirth.
31. Torres R, Soltero S, Trak MA, Tucker CM, Mendez K, Campos M, et al. Lifestyle modification intervention for overweight and obese Hispanic pregnant women: development, implementation, lessons learned and future applications. Contemp Clin trials Commun [Internet] 2016 [cited 2017 Jan 22];3:111-6. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2451865416300175. DOI: 10.1016/j.conctc.2016.05.004
32. Institute of Medicine (IOM). Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: The National Academy Press; 2011.
33. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin d deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-30. DOI: 10.1210/jc.2011-0385
34. Goodman SN. A comment on replication, P-values and evidence. Stat Med [Internet] 1992 [cited 2020 Jun 29];11:875-9. Available from: https://pubmed.ncbi.nlm.nih.gov/1604067/. DOI: 10.1002/sim.4780110705
35. Pérez ME, Pericchi LR. Changing statistical significance with the amount of information: The adaptive α significance level. Stat Probab Lett [Internet] 2014 [cited 2020 Jun 29];85:20-4. Available from: https://pubmed.ncbi.nlm.nih.gov/24511173/.
36. Figueiredo ACC, Cocate PG, Adegboye ARA, Franco-Sena AB, Farias DR, de Castro MBT, et al. Changes in plasma concentrations of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D during

pregnancy: a Brazilian cohort. Eur J Nutr [Internet] 2018 [cited 2019 Feb 1];57:1059-72. Available from: http://link.springer.com/10.1007/s00394-017-1389-z. DOI: 10.1007/s00394-017-1389-z

37. Bouillon R, Van Assche FA, Van Baelen H, Heyns W, De Moor P. Influence of the vitamin D-binding protein on the serum concentration of 1,25-dihydroxyvitamin D3. Significance of the free 1,25-dihydroxyvitamin D3 concentration. J Clin Invest [Internet] 1981 [cited 2019 Jan 31];67:589-96. Available from: http://www.jci.org/articles/view/110072. DOI: 10.1172/JCI110072

38. Holmes VA, Barnes MS, Alexander HD, McFaul P, Wallace JMW. Vitamin D deficiency and insufficiency in pregnant women: a longitudinal study. Br J Nutr [Internet] 2009 [cited 2019 Jan 29];102:876. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19331703. DOI: 10.1017/S0007114509297236

39. Lain KY, Catalano PM. Metabolic Changes in Pregnancy. Clin Obstet Gynecol [Internet] 2007 [cited 2019 Feb 1];50:938-48. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17982337. DOI: 10.1097/GRF.0b013e31815a5494

40. Napso T, Yong HEJ, Lopez-Tello J, Sferruzzi-Perri AN. The Role of Placental Hormones in Mediating Maternal Adaptations to Support Pregnancy and Lactation. Front Physiol [Internet] 2018 [cited 2019 Feb 1];9:1091. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30174608. DOI: 10.3389/fphys.2018.01091

Table I. Socio-demographic and health history variables

Variable	Mean ± SD / n (%)
Maternal age, years	27.7 ± 5.5
Race	
Black/African American	8 (25.8)
White	7 (22.6)
Other	16 (51.6)
Hispanic	31 (100)
Educational level	
High School education/diploma or less	15 (48.4)
College education	16 (51.6)
Total Annual Family Income	
≤ $ 9,999	14 (45.2)
$ 10,000-$ 19,999	11 (35.4)
≥ $ 20,000	6 (19.4)
Gestational age at enrollment (weeks)	13.8 (2.5)
Gestational length (weeks)	37.1 (3.3)
Parity	
Primiparous	9 (29.0)
Multiparous	22 (71.0)
Enrollment BMI (kg/m^2)	35.3 ± 7.4
Prior gestational diabetes mellitus	2 (5.4)
Use of dietary supplements early in pregnancy	
Prenatal supplements	14 (45)
Vitamin D supplements	0
Infant birth weight (g)	2787 ± 789

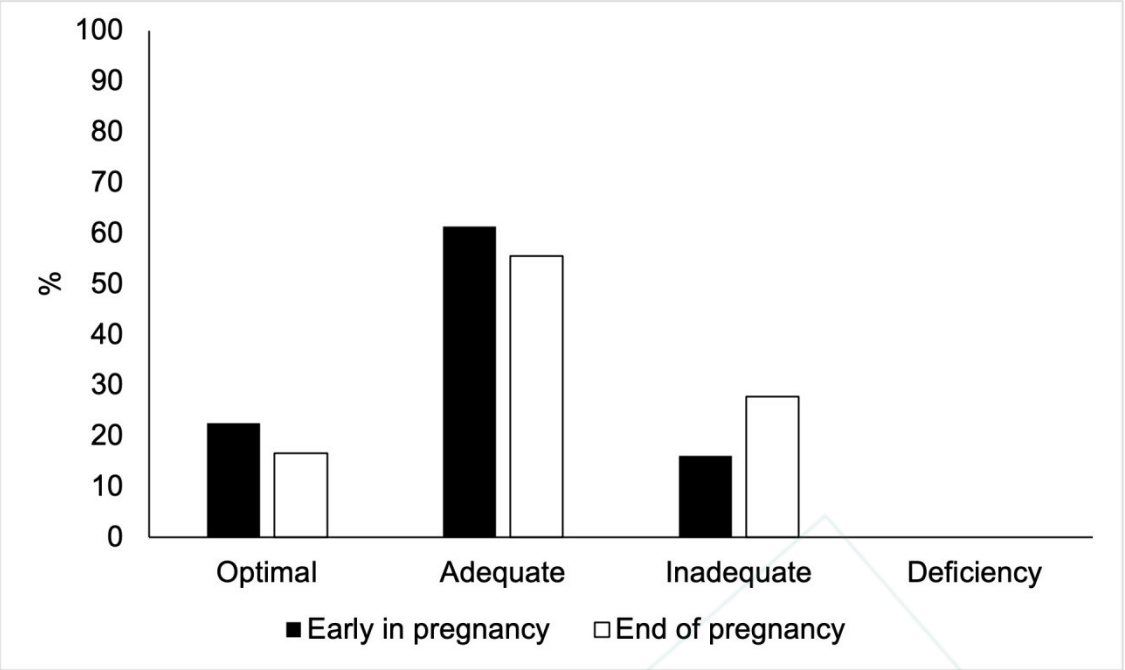

Fig. 1. Maternal vitamin D status early in pregnancy and at the end of pregnancy* (*McNemar's Chi-squared value, 1.33; p-value = 0.72).

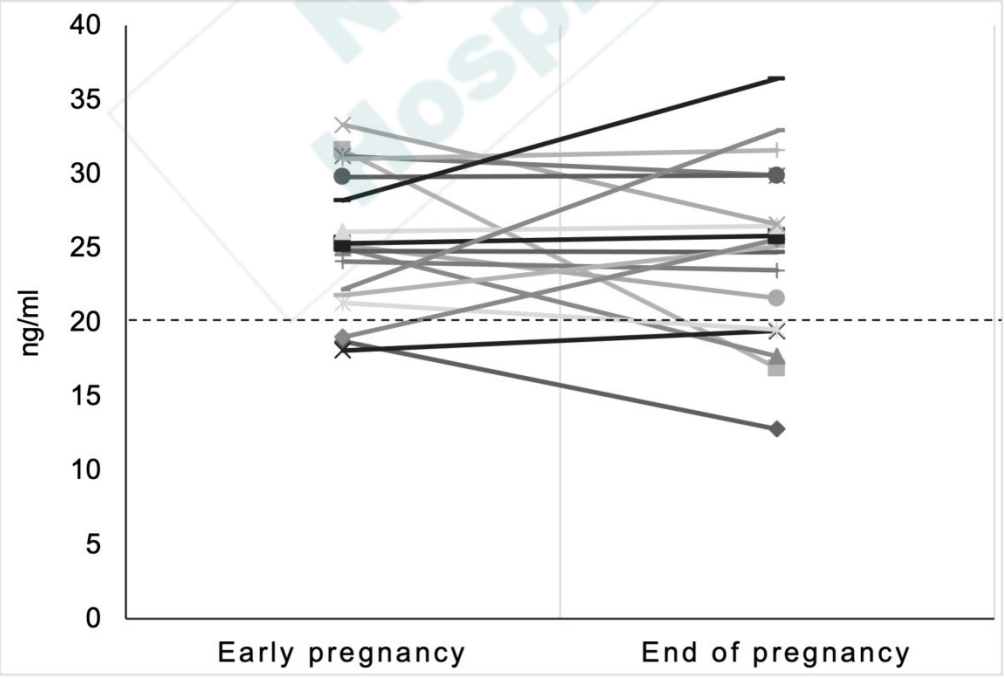

Fig. 2. Individual change in 25(OH)D levels during pregnancy (mean changes in serum 25(OH)D levels were not significant between early (25.2 ± 5.8 ng/mL) and late pregnancy (24.8 ± 6.1 ng/mL); mean difference 95 % CI, -2.38, 3.53; paired t-test: t-value, 0.41, p-value = 0.69; dotted line represents adequate level).

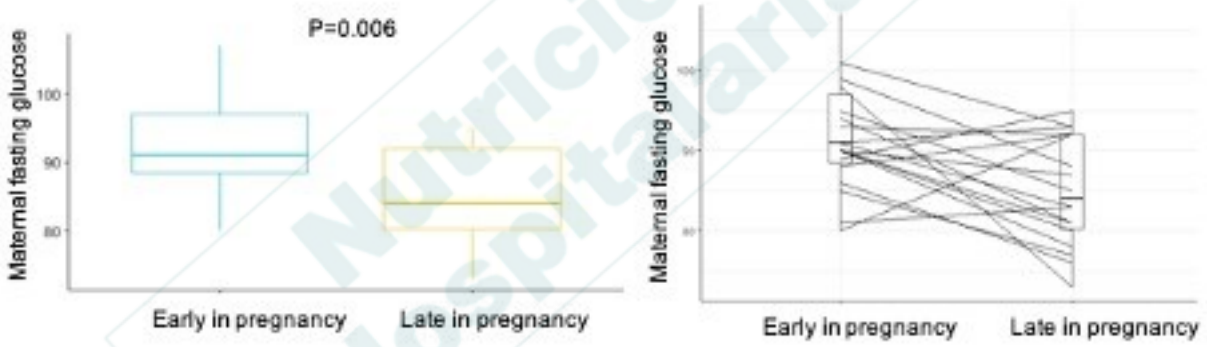

Fig. 3. Glucose levels during pregnancy (right-tail paired t-test t-value, 2.784; p-value = 0.006; mean difference 95 % CI, 2.125, Inf; two-tail paired t-test t-value, 2.784; p-value = 0.013; mean difference 95 % CI, 1.372, 9.961).

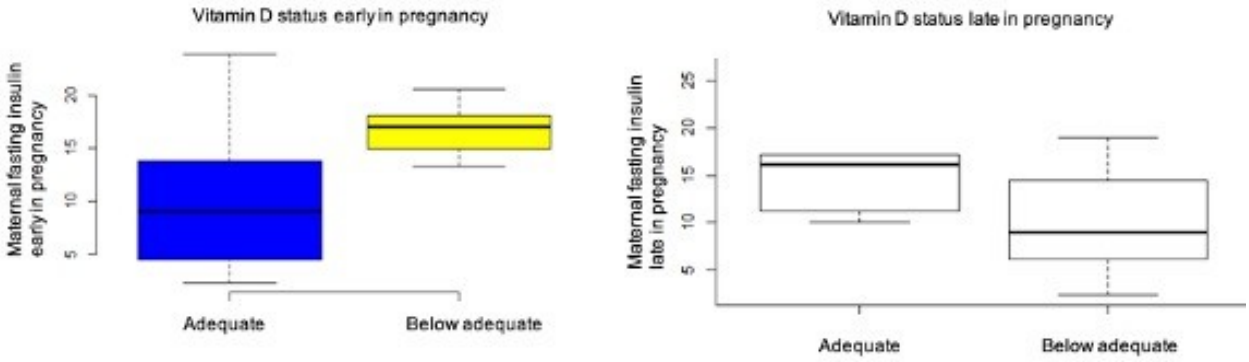

Fig. 4. Insulin levels by vitamin D status (two-tailed t-test for early in pregnancy: $p < 0.01$ with t-value, -3.93 and 95 % CI, -10.5, -3.04; two-tailed t-test for late in pregnancy: $p = 0.11$ with t-value, 1.90 and 95 % CI, -2.18, 15.7).

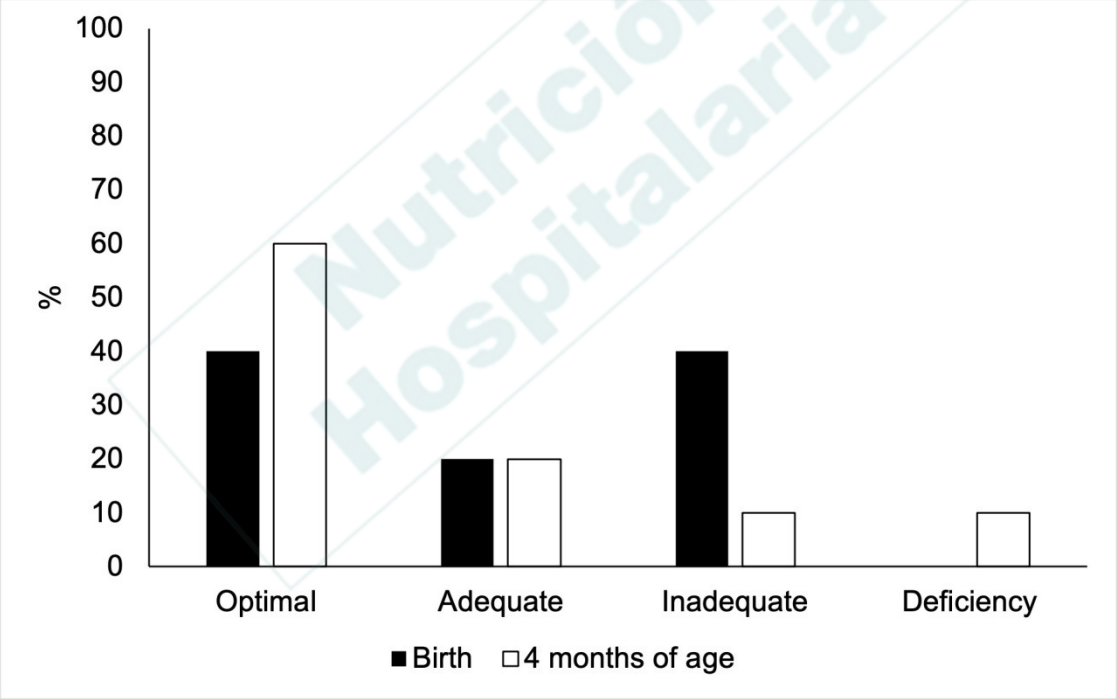

Fig. 5. Infant vitamin D status at birth and at 4 months of age* (*not statistically significant; $Chi^2 = 2.90$, $p = 0.996$).