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Symptomatic Hypocalcemiain Neonates Due to Maternal Hypovitaminosis D in Rural Tertiary Care Center: A Case Series

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Vitamin D deficiency in neonates is not uncommon and is characterized by severe hypocalcemic symptoms. In babies with poor vitamin D resources, calcium, phosphorus, and homeostasis are affected, leading to neonatal hypocalcaemia clinical manifestations. Newborn babies with vitamin D deficiency are at risk of deficiency and hypocalcaemia. Therefore, vitamin D supplementation in pregnant and lactating mothers should be routinely considered. Of newborns with symptomatic hypocalcaemia admitted in Level III NICU in the rural part of western Maharashtra from October 2019 to September 2020 were reviewed. These babies were admitted to NICU due to several illnesses, including suspected sepsis, tachypnea, jaundice, etc. They were investigated for sepsis screen including Complete Blood count, CRP, Blood culture, CSF analysis. Cranial USG through anterior fontanelle and Neuro imaging and Electroencephalogram were done wherever necessary. This study intends to highlight the manifestation of maternal hypovitaminosis D on the mother and its effects on the neonate. Maternal hypovitaminosis leads to neonatal hypovitaminosis D and can present as hypocalcaemia.

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1. INTRODUCTION

The deficiency of Vitamin D has been a matter of increasing interest. Recently, Vitamin D deficiency in mothers is an important area of study [1]. Maternal vitamin D status determines newborn vitamin D status. Recently, a lot of research has been done to determine the role of Vitamin D on the feto-placental unit. Several research studies have been done on maternal serum in white women [2]. Apart from the classical action on bone metabolism, including calcium balance, non-classical roles such as effect on insulin secretion and its action, immune-modulation, development of lung have been identified. Hypocalcaemia is a metabolic manifestation of vitamin D deficiency in neonates and is a potentially life-threatening condition. Neonatal hypocalcaemia can be classified into – Early-onset (within the first 72 hours) and Late-onset (after 72 hours) [3]. The cause of late-onset neonatal hypocalcaemia is predominantly vitamin D deficiency and the cause of vitamin D deficiency at this particular period is a maternal deficiency [4]. In India, where the commonness of vitamin D deficiency is high, vitamin D supplementation of vitamin D at two levels that is maternal vitamin D supplementation to women during pregnancy [5] and early vitamin D supplementation to new-borns is essential to avoid complications of hypocalcaemia [6] in neonates and skeletal abnormalities in growing infants [7].

There is a paucity of data on intake of vitamin D during pregnancy and also during lactation. This study intends to highlight the manifestation of maternal hypovitaminosis D on the mother and its effects on the neonate. Maternal hypovitaminosis [8] D leads to neonatal hypovitaminosis D and can present as hypocalcaemia. Neonatal hypocalcaemia [9] is usually asymptomatic but can have many non-specific symptoms like lethargy, vomiting, jitteriness, abdominal distension, poor muscle tone, and refusal to feed. It can have life-threatening manifestations like convulsions, apnoea, conduction abnormalities, bradycardia, and arrhythmias, worsening of PPHN, coagulation defects, and platelet dysfunction [10].

We present a case series of newborn babies with symptomatic hypocalcaemia admitted to Level III NICU in rural part of western Maharashtra.

2. METHODOLOGY

The records of newborns with symptomatic hypocalcaemia admitted in Level III NICU in a rural part of western Maharashtra from October 2019 to September 2020 were reviewed. These babies were admitted to NICU due to several illnesses, including suspected sepsis, tachypnea, jaundice, etc. They were investigated for sepsis screen including Complete Blood count, CRP, Blood culture, CSF analysis. Table 1 shows the vitamin D status. Cranial USG through anterior fontanelle and Neuro imaging and Electroencephalogram were done wherever necessary. The cardiac evaluation was also done when indicated, including ECG 2D ECHO [11]. Hypocalcaemia was detected by initial blood chemistry and repeat workup done as per protocol. After the diagnosis of hypocalcaemia, the serum of the baby and mother were collected for 25-OHD. Other necessary investigations were sent as per protocol or reports collected from laboratory data.25-OHD levels of new born and mother were measured using enzyme-immunoassay.

Table 1. Classification -vitamin D status

25-OH Vitamin D (ng/ml)	Status
≤10	Deficiency
10 to 20	Insufficiency
>20	Normal

Normal ranges of laboratory parameters are mentioned in Table 2.

2.1 Case Series

Case 1:

A 7 Day old baby, a non-consanguineous marriage product, on exclusive breastfeeding and thriving well was convulsions that were generalized and without encephalopathy. The baby had multiple such episodes. The baby was euthermic and euglycemic at admission. Septic screen, CSF analysis, serum electrolytes were within normal limits, and USG brain, Electroencephalogram, and 2D ECHO were also normal. Metabolic workup showed hypocalcaemia with Ionic calcium levels of 0.76 mmol/L; Serum Magnesium was low, Serum Phosphorus and PTH levels were high normal. The baby was treated with Intravenous 10 % Calcium Gluconate and 50% Magnesium

Sulphate. On Investigating further, 25OHD (Vit D) level was very low, 7.6 ng/ml. Maternal investigations were done to find the cause of vitamin D deficiency. The mother showed hypovitaminosis D with vitamin D levels 5.6 ng/ml. The baby was treated with vitamin D, calcium supplements in therapeutic doses. On follow up calcium and vitamin D levels were normalized. The baby was healthy and seizure-free on discharge and at subsequent follow-up.

Case 2:

A 10-day old baby presented with poor feeding, lethargy, and abnormal body movements (convulsions) perceived by the mother at home. The baby was jittery on admission. The baby was euthermic, and blood sugar levels were normal. Investigations were suggestive of low serum and ionic calcium 0.7 mmol/l, and vitamin D was very low, 4.8 ng/ml. Other investigations, including Neurosonogram, septic screen, Serum electrolytes, Magnesium, were normal. The baby was treated with IV Calcium Gluconate and oral vitamin D in therapeutic doses. When the mother was investigated, she also had a vitamin D deficiency with a vitamin D level of 8 ng/ml. The baby remained seizure-free after that and was discharged on oral supplements.

Case 3:

A 3-day old baby was shifted to NICU from the postnatal ward due to sudden development of tachypnea and feeding difficulties. On examination, the baby had bradycardia. ECG showed sinus bradycardia, and 2D ECHO was normal. Other investigations, including Septic screen, blood sugars, and serum electrolytes, were normal. Serum calcium was low 6 mg/dl, and Ionic calcium was 0.79 mmol/L. Serum Magnesium was within normal limits. The baby was treated with Intravenous 10% Calcium Gluconate with intense cardiac monitoring. Heart rate was stabilized in a couple of days after initiating calcium treatment, and repeat Ionic calcium was found normal. On investigating further, the baby had vitamin D levels 4.8 ng/ml, and the mother was also found to be deficient with vitamin D levels 8.9 ng/ml. Both baby and mother were started on oral calcium and vitamin D supplements. The baby was discharged in stable condition and followed up regularly.

Case 4:

A 3-day old baby, full-term, delivered vaginally, was admitted to NICU with presenting complaints of refusal to feed. The baby had apnea and bradycardia. Intravenous caffeine started with high-flow oxygen. There was no history suggestive of perinatal asphyxia. IVO bradycardia ECG and 2D ECHO was done. ECG was suggestive of Sinus bradycardia, and 2D ECHO was normal. USG Brain, septic screen, serum electrolytes were normal. On metabolic screening, the baby had hypocalcaemia (Ionic Calcium 0.83 mmol/L) and hypovitaminosis [11] D (5.8ng/ml) serum magnesium was normal. Mother's deficiency of vitamin D(6ng/ml). Calcium and vitamin D supplements were continued for the baby, gradually, bradycardia and apneas subsided, and that corresponded to improved levels of ionic calcium. Baby and mother were sent home with oral calcium and vitamin D supplements.

Case 5:

A 38 years old primigravida delivered a baby with a birth weight of 2.9 kg with me conium-stained liquor. Baby delivered by emergency LSCS due to fetal distress and placenta previa. The baby cried immediately after birth but had respiratory distress and grunting. The neonate was started on CPAP in the delivery room, and CPAP was continued in NICU. The baby had Me conium Aspiration Syndrome with Persistent Pulmonary Hypertension treated with CPAP, in tropes, and Sildenafil. But despite other clinical improvements, the baby lingered on oxygen, and it was difficult to wean it off. 2D ECHO and other investigations were all normal apart from hypocalcaemia and hypovitaminosis D. Baby was treated with IV calcium Gluconate and oral Vitamin D in therapeutic doses. The mother's vitamin D levels were low at 9.6ng/ml. She was also started on supplements. We were able to wean off oxygen in a couple of days, and the baby was discharged.

Case 6:

A 7 day old baby, near term, small for gestational age, on exclusive breastfeeding, was admitted to NICU with a history of vomiting, lethargy, and refusal to feed. The baby was febrile and dehydrated on admission and was euglycemic. Investigations revealed hypernatremia (Sodium 150 meq/L) and hypocalcaemia. Urea/Creatinine was normal; the septic screen was negative, CSF analysis normal. The baby was given fluid correction and calcium supplements. Sodium and dehydration were corrected, but the baby still had persistent hypocalcaemia. On further workup,

Magnesium and phosphorus levels were normal, but vitamin D levels were very low, 4.2ng/ml. maternal blood levels of vitamin D were also deficient 5.2ng/ml. Both the baby and mother were given oral calcium and vitamin D supplements.

Case 7:

Another baby was admitted to NICU on Day 4 with similar vomiting, refusal to feed, lethargy. The baby was a febrile and euthermic but was found to have hypocalcaemia and hypovitaminosis D [12]. The mother also had hypovitaminosis D. Both the baby and the mother were given calcium and vitamin D supplements.

3. RESULTS AND DISCUSSION

We selected seven cases of symptomatic hypocalcaemia, and their data were collected and analyzed as shown in Table 2. Calcium is one of the most plentiful minerals in our body and essential for various biochemical and physiological functions in the body. Hypocalcaemia in neonates can be asymptomatic or manifest from non-specific symptoms like refusal to feeds, lethargy to life-threatening convulsions and conduction defects, including arrhythmias. In our case series of seven cases, two babies presented with convulsions, one baby had bradycardia and tachypnea, one baby presented with apnoea and bradycardia, which responded to calcium and vitamin D treatment, one baby had persistent pulmonary hypertension despite treatment and hypocalcaemia worsened PPHN. Two babies presented with vomiting, refusal to feeds, lethargy, and responded to calcium and vitamin D treatment.

Hypovitaminosis D in the mother is the major cause of hypocalcaemia in neonates, especially late-onset. Late-onset neonatal hypocalcaemia can be defined as hypocalcaemia that is developed after three days. In our case series, all babies presented with late-onset neonatal hypocalcaemia that is after D3 of life. Two babies had associated hypomagnesaemia, and PTH levels were high normal. All babies had serum phosphorous levels within normal limits. On the evaluation of vitamin D status, all babies had low Vitamin D levels. In our case series, neonatal late-onset hypocalcaemia and neonatal vitamin D deficiency were due to hypovitaminosis D in the mother.

Table 2. Investigation chart of babies with symptomatic hypocalcaemia

Sr. No	DOL	Presenting Symptoms	Serum calcium (mg/dl) Ionic calcium (mmol/L)	25-OH-Vitamin D(ng/ml)	Serum Magnesium (mg/dl)	Maternal Vitamin D (ng/ml)
			8.5-10.5 mg/dl 1-1.35mmol/L	20-50 ng/ml	1.7-2.4 mg/dl	20-50 ng/ml
1	Day 7	Convulsion	5.8 mg/dl 0.76 mmol/L	7.6	1.33	5.6
2	Day 5	Poor feeding, Jitteriness, Convulsion	5.39 mg/dl 0.7 mmol/L	4.8	1.67	8
3	Day 3	Bradycardia, Tachypnea	6 mg/dl 0.79 mmol/L	4.8	1.8	8.9
4	Day 4	Feeding difficulties Bradycardia, Apneas	6.4 mg/dl 0.83 mmol/L	5.8	2	6
5	Day 3	Tachypnea, Refusal to feed pulmonary Hypertension	7.8 mg/dl 0.98 mmol/L	4.6	2	9.6
6	Day 7	Lethargy, refusal to feed, vomiting	5.54 mg/dl 0.72 mmol/L	4.2	2.1	5.2
7	Day 4	Refusal to feed, vomiting, Lethargy	6.8 mg/dl 0.88 mmol/L	8.1	1.72	5

Neonatal vitamin D deficiency may present as symptomatic hypocalcaemia as neonatal seizures; in 85 % of babies with hypocalcaemia seizures mother was also deficient. In a study in Egypt, 100 % of mothers of infants who had seizures due to hypocalcaemia had very low vitamin D. Hypovitaminosis D in mothers affects the growth and development of bones in fetal life. Maternal Vitamin D deficiency also causes bone demineralization and increases chances of fractures, hyper reactive airway disease in babies, and increases incidences of RSV viral infections.

Vitamin D deficiency is a public health issue in India. Even though there is enough sunlight in most of the subcontinent, the growing rates of hypovitaminosis dare alarming. The prevalence of hypovitaminosis D is around 50-90% in India. The prevalence among pregnant women is around 42-74%.

The various factors that can contribute to causing hypovitaminosis D include inadequate dietary intake, lack of routine supplementation, and increased prevalence among Asian ethnicity. Apart from these factors, obesity is related to increased hypovitaminosis D levels during pregnancy and in neonates [13]. According to the Royal College of Obstetrics and Gynaecology, 61 % of obese women (Body Mass Index > 30kg/m2) before conception were vitamin D deficient instead of only 36% with a pregnancy BMI < 25 kg/m2. Out of the seven women studied, four were found to be obese in our series [14].

Various complications due to hypovitaminosis D have been studied. During pregnancy, it can cause the development of impaired glucose tolerance. Although hypovitaminosis D has been linked with the development of Gestational Diabetes Mellitus [15], the evidence is not clear. Among the seven women studied, two were diagnosed with GDM in our study.

Development of low birth weight is also a documented finding inadequate of vitamin D.A research conducted in Holland showed 2.4-fold risk of Short for gestational age in mothers with low levels of vitamin D. Similarly in a study from Australia shows 200 g lower mean birth weight in mothers with deficiency of vitamin D. Some other studies suggested that third-trimester vitamin D deficiency is more related to low birth weight than in the early period of pregnancy and also increased chances of preterm delivery. According to studies, caesarean section rates are increased in vitamin D deficient mothers, but the cause remains unknown.

Daily oral vitamin D supplementation, namelycholecalciferol or ergocalciferol, is safe during pregnancy. All pregnant women should be made aware of the need for supplementation and the harmful effects of hypovitaminosis D. As per NICE guidelines, pregnant women should take 400 IU, i.e., ten mcg vitamin D supplements daily. These guidelines also recommend that high-risk women with high risk, like those with skin pigmentation, less sunlight exposure, or obesity, should be supplemented with 1000IU / day. Women with a risk of developing pre-eclampsia should take 800 IU/day. Vitamin D should be started preferably at birth 400 IU/day to all newborns and continued till one year of life.

Routine screening of Vitamin D and in infancy is not recommended at the time of pregnancy. Some studies propose routine testing in high-risk women. However, as the test is expensive and not easily available, offering universal supplementation is a cost-effective alternative, especially in rural India. Measurement of vitamin D levels should be continued in symptomatic hypocalcaemia women along with their management.

4. CONCLUSION

Symptomatic late-onset hypocalcaemia is mostly due to maternal hypovitaminosis D. Preventative measures to avoid shortage of vitamin D among pregnant women and newborns should be adopted. Calcium, vitamin D, and oral vitamin D supplementation in neonates since birth might include intake of pregnant and nursing women. In our case study, all newborns with late-onset, neonatal hypocalcemia that occurs after life D3 should have dietary enhancements by the public health department. The related hypomagnesaemia was seen in two infants and PTH levels were elevated. In normal conditions, all children have serum phosphorus levels. Symptomatic late-onset hypocalcaemia is primarily due to maternal hypovitaminoid D. Prevention methods for preventing vitamin D insufficiency in pregnant moms and newborns should be undertaken. Calcium and vitamin D may also have been consumed by women who are pregnant and breast feeding and neonates have been supplemented with oral vitamin D. In

our case study, all newborns with late-onset, neonatal hypocalcemia that occurs after life should have vitamin D3 dietary enhancements by the public health department. Two children had hypomagnesaemia and high normal PTH levels. All infants were in the normal range of serum levels.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical approval taken from symbiosis Medical College for Women, Symbiosis International (Deemed University), Pune, Maharashtra, India.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. 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. 2013;346: f1169.
2. Bodnar LM, Catov JM, Zmuda J. M., Cooper, M. E., Parrott, M. S., Roberts JM, Simhan HN. Maternal serum 25-hydroxyvitamin D concentrations are associated with small-for-gestational-age births in white women. The Journal of nutrition. 2010;140(5):999-1006.
3. Wei SQ, Qi HP, Luo ZC, Fraser WD. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. The Journal of Maternal-Fetal & Neonatal Medicine. 2013; 26(9):889-899.
4. Dave A, Verma M, Jain N, Dave A. A study of vitamin D levels and associated deficiency in pregnancy and its effect on maternal and fetal outcome. Int J Reprod Contracept Obstet Gynecol. 2017;6: 84-8.
5. Bowyer L, Catling-Paull C, Diamond T, Homer C, Davis G, Craig ME. Vitamin D, PTH and calcium levels in pregnant women and their neonates. Clinical Endocrinology. 2009;70(3): 372-7.
6. Do HJ, Park JS, Seo JH, Lee ES, Park CH, Woo HO, Youn HS. Neonatal late-onset hypocalcemia: is there any relationship with maternal hypovitaminosis D?. Pediatric gastroenterology, hepatology & Nutrition. 2014; 17(1):47.
7. Camargo Jr CA, Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, Kleinman K, Gillman MW. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. The American journal of clinical nutrition. 2007;85(3):788-95.
8. Pandey A, Prakash G. Deduplication with Attribute Based Encryption in E-Health Care Systems. International Journal of MC Square Scientific Research. 2019;11(4): 16-24.
9. Jain A, Agarwal R, Sankar MJ, Deorari A, Paul VK. Hypocalcaemia in the newborn. The Indian Journal of Pediatrics. 2010 Oct; 77(10):1123-8.
10. KhalesiKhalesi N, Bahaeddini SM, Shariat M. Prevalence of maternal vitamin D deficiency in neonates with delayed hypocalcaemia. ActaMedicaIranica. 2012; 740-5.
11. Thomas SD, Fudge AN, Whiting M, Coates PS. The correlation between third-trimester maternal and newborn-serum 25-hydroxy-vitamin D in a selected South Australian group of newborn samples. BMJ open. 2011 Jan 1; 1(2).
12. Mehrotra P, Marwaha RK, Aneja S, Seth A, Singla BM, Ashraf G, Tandon N. Hypovitaminosis d and hypocalcemic seizures in infancy. Indian Pediatrics. 2010;47(7): 581-586.
13. Leffelaar ER, Vrijkotte TG, van Eijsden M. Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort. British Journal of Nutrition. 2010 Jul; 104(1):108-17.
14. Morley R, Carlin JB, Pasco JA, Wark JD. Maternal 25-hydroxyvitamin D and parathyroid hormone concentrations and offspring birth size. The Journal of Clinical

Endocrinology & Metabolism. 2006;91(3): 906-12.
15. Makgoba M, Nelson SM, Savvidou M, Messow CM, Nicolaides K, Sattar N. First-trimester circulating 25-hydroxyvitamin D levels and development of gestational diabetes mellitus. Diabetes Care. 2011; 34(5):1091-3.

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