Vitamin D depletion in pregnancy decreases survival time, oxygen saturation, lung weight and body weight in preterm rat offspring

Lykkeåsgaard S1,2, Sorensen GL1, Beck-Nielsen SS1,2, Pilecki B1, Duelund L1, Marcussen N2, Christensen HT1,2
1Hans Christian Andersen Children’s Hospital, Odense University Hospital, Odense, Denmark. 2Clinical Institute, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark. 3Institute of Molecular Medicine, Department of Cancer and Inflammation, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark. 4MEMPHYS, University of Southern Denmark, Odense, Denmark. Institute of Pathology, Odense University Hospital, Odense, Denmark.

CONCLUSION

Vitamin D depletion during pregnancy led to a lower SaO2 and shorter survival-rate in premature rat offspring despite no reduction in lung surfactant constituents. Explanatory factors include reduced lung weight, implying a reduced total lung diffusion area, and decreased birth weight, which may indicate a reduced muscle mass leading to earlier muscular fatigue.

OBJECTIVES

1. To test if vitamin D depletion aggravates respiratory insufficiency in preterm rat offspring.
2. To assess the effects of vitamin D depletion on growth and lung surfactant production.

BACKGROUND

In vivo studies in rodents have shown that vitamin D deficiency during pregnancy causes alterations in lung growth and structure in term offspring. In vitro studies of cells from fetal rat lung explants have shown an effect of vitamin D on the embryogenesis and cellular growth and differentiation, including surfactant synthesis and secretion. Laboratory studies on human pulmonary adenocarcinoma-derived cell lines support these findings. However, in vivo studies of the role of vitamin D in lung development in preterm offspring have not been performed.

METHODS

Female Sprague-Dawley rats were randomly assigned low vitamin D (VD3) or control diet for at least 5 weeks before mating and followed with serum 25-hydroxyvitamin D (s-25(OH)D) measurements.

After cesarean section at gestational day 19 (E19) or day 22 (E22), placental weight (PW), birth weight (BW), crown-rump-length (CRL), oxygenation (SaO2) at 30 min and survival time were recorded.

The lungs from the pups were analyzed for phospholipid levels, surfactant protein A-D mRNA and the expression of the vitamin D receptor (VDR).

RESULTS

- S-25(OH)D was significantly lower in the VD3 group at cesarean section (12 vs. 30nmol/L, p<0.0001).
- All mother rats achieved a weight gain during the experiment with no significant difference in gestational weight gain between the groups. At the cesarean section, no differences were observed in maternal SaO2, the duration of maternal anesthesia or in the number of pups in each litter.
- When comparing preterm and term offspring in general, a significant difference was observed in all measurements (lung, birth and placental weights and CRL) as the results of maturation.

RESULTS, et al.

- At E19, VD3 pups had a lower birth weight (2.13 vs. 2.29g, p<0.001), lung weight (0.09 vs. 0.10g, p=0.002), SaO2 (54% vs. 69%, p=0.002) as well as reduced survival time (0.50 vs. 1.25h, p<0.0001) compared to the controls (fig. 1 and 2).
- At E22, the VD3-induced pulmonary differences were leveled out, but VD3 pups had lower CRL (4.0 vs. 4.5cm, p<0.0001).
- The phospholipid levels and the surfactant protein mRNA expression did not differ between the dietary groups, nor did the expression of the VDR.

PERSPECTIVES

Our study emphasizes the value of animal models to study the effects of vitamin D on the lungs. Aggravation of respiratory failure may occur due to reduced lung and birth weight as the result of severe vitamin D depletion. However, we were unable to show a direct effect of vitamin D deficiency on surfactant measures or VDR expression.

Future studies should pursue to evaluate our results using an optimized version of our model with animals assigned to the diets immediately after weaning.

ACKNOWLEDGEMENTS & FOUNDING

- Thank you to animal technician Anne Mette Durand and medical student Kathrine Work Havelund.
- Financial support: Dagmar Marshalls foundation, Aase & Ejner Danielsen foundation, Takeda Pharma, The A.P. Moeller Foundation for the Advancement of Medical Science and Odense University Hospital.

Disclosure statement: The authors have no conflicts of interest.