

## Review Article

# Importance of vitamin D supplementation in pregnancy-review

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### ABSTRACT

Pregnancy is a state that leads to several deficiency and increased demand of essential nutrients for the growing foetus. In one such case it is seen that vitamin D deficiency can lead to severe outcome in the new-born as well as the mother. Vitamin D travels to the foetus by passive transfer and the foetus is entirely dependent on maternal stores. Therefore it becomes all the more essential to know your vitamin D level during antenatal period to prevent adverse outcomes. Vitamin D supplementation helps in preventing the outcomes like rickets, low birth weight, bone and dental deformity in foetus, decreased immunity and impaired lung function in children, whereas also helping in decreased incidence of primary caesarean sections, preeclampsia, gestational diabetes mellitus in mother. The recommended dose has been described up to 2000IU/day as a supplementation and not therapeutic dose, which is found to be safe and effective.

**Keywords:** Vitamin D, Pregnancy, Supplementation

### IMPORTANCE OF VITAMIN D IN PREGNANCY

Obstetric endocrinology is a field known for opportunity, challenges and caution. Opportunity, because the antenatal period is a time during which endocrine and metabolic manipulation can impact not only maternal and foetal health, but also long-term outcomes in offspring. The rapidly increasing incidence of endocrine dysfunction in obstetrics, and the public health importance of these conditions, requires more attention.<sup>1</sup> Vitamin D supplementation during pregnancy has been suggested as an intervention to protect against adverse gestational and neonatal outcomes.

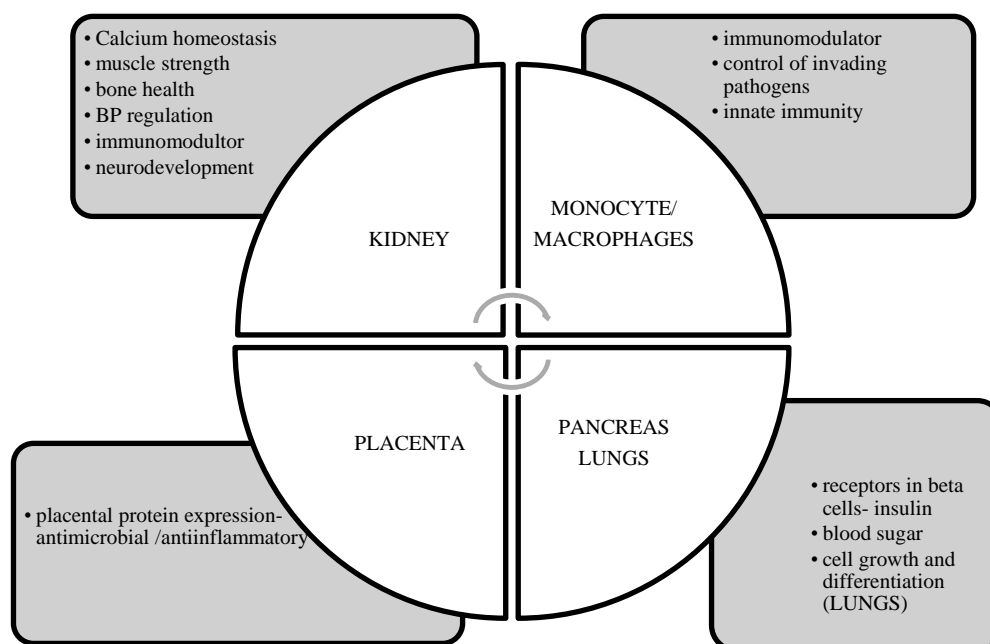
### VITAMIN D DEFICIENCY CONSEQUENCES IN PREGNANCY

Large studies have revealed the high prevalence of vitamin D deficiency in women, including both antenatal and lactating mothers.<sup>4-6</sup> The physiological rise in the

active metabolite, the enhanced intestinal calcium absorption, and enhanced foetal requirement of calcium all point to the importance of vitamin D biology in pregnancy.<sup>7</sup>

There is relationship between low vitamin D and adverse maternal outcomes such as recurrent pregnancy loss, primary caesarean section and postpartum depression preeclampsia and eclampsia.<sup>8-17</sup> Other authors have described the association of maternal vitamin D deficiency with asthma and impaired lung function in offspring.<sup>18-21</sup> Impaired immune response preterm birth gestational diabetes.<sup>2,3,8,15,18,23,24,26-28</sup>

In a study a trend toward a higher risk of type 1 diabetes with lower levels of vitamin D during pregnancy has been found. The odds of type 1 diabetes was more than twofold higher for the offspring of women with the low levels of 25-OH D compared with the offspring of those with higher levels of vitamin D.<sup>1</sup>



**Figure: Role of vitamin D in pregnancy.<sup>2,3</sup>**

### RECOMMENDED DAILY DOSE ACCORDING TO RESEARCH

The institute of medicine recommendations suggest a normal level of 20 ng/ml in pregnancy, while the endocrine society recommends 30 ng/ml or more.<sup>29,30</sup> A circulating level of 25-hydroxyvitamin D of >75 nmol/l, or 30 ng/ml, is required to maximize beneficial effects of vitamin D on health.<sup>31</sup>

The recommended daily intake of vitamin D ranges from 400 to 600 IU (by the IOM) 400 IU (by the National Institute for Health and Clinical Excellence, United Kingdom) and to 1500-2000 IU (by the endocrine society) and 2000 IU (by the Canadian society).<sup>32-35</sup> Trend analysis studies indicate that offspring may benefit from approximately 800 IU/d vitamin D intake during pregnancy.<sup>20</sup> Studies with 4000 IU/day of vitamin D has shown safety and efficacy.<sup>36</sup> An RCT data indicate that 4,000 IU/day vitamin D supplementation during pregnancy will make sure normal vitamin D level is maintained in the body and improve birth outcomes with no risk of side effects.<sup>4,10</sup>

Holles et al showed in his study that vitamin D after first trimester in antenatal women i.e. 12 weeks later benefitted in primary caesarean sections, hypertensive cases, and other problems.<sup>37</sup> Dawodu et al had shown in his study using 2000IU and 4000IU/day intake of vitamin D supplementation after gestational age of 12 weeks on Arab pregnant women from vitamin D deficient areas with better outcome and safety.<sup>38</sup>

Similar study from New Zealand showed that 2000 IU/day at 27 weeks and continuing it at a dose of 800

IU/day till the infant is of 6 months of age have resulted with better pregnancy outcomes.<sup>39</sup>

Vitamin D supplementation with doses of 2000 IU/d or lower during pregnancy may reduce the risk of foetal or neonatal mortality.<sup>30</sup> In the absence of adequate sun exposure, at least 800-1000 IU Vitamin D3 may be needed to achieve better outcome in children and adults.<sup>31</sup> Vitamin D supplementation with doses of 2000 IU/d or lower during pregnancy may reduce the risk of foetal or neonatal mortality.<sup>40</sup>

### BENEFITS OF VITAMIN D SUPPLEMENTATION

The benefits of vitamin D supplementation is seen in both the mother and child—the dual benefit is discussed separately for mother and child.

In the child the main benefits seen and observed in various studies are:

#### *Preterm*

Vitamin D supplementation in pregnancy reduces the risk of preterm birth by 64%.<sup>27</sup> Relation of maternal status of vitamin D and supplementation in preventing preterm birth was also seen in other studies.<sup>18,25,26</sup>

#### *Birth weight and anthropometry*

Vitamin D is a major contributor in bone mineralisation which helps in the bone development of the growing foetus. Intra-uterine growth retardation was seen to be lower and with better anthropometry in the new born of the pregnant women taking supplementation of vitamin D as compared to those pregnant women who did not take

any vitamin D. These differences persisted until 9 months of age.<sup>40</sup> Supplementing pregnant women with vitamin D in a single or continued dose increases serum 25-hydroxyvitamin D at term, this led to reduced number of low birth weight in new born.<sup>26</sup> Normal 25 (OH) D level in later pregnancy above 32 gestational weeks showed a better birth weight and neonatal anthropometry (length).<sup>41</sup> Vitamin D regulates genes responsible for trophoblastic invasion and angiogenesis critical for placental implantation and function which is important for foetal growth.<sup>29</sup> Vitamin supplementation in pregnancy reduces the risk of low birth weight (2500 g) by 60%.<sup>27</sup> Vitamin D supplementation during pregnancy is associated with a reduced risk of SGA and improved infant growth without risk of foetal or neonatal mortality or congenital abnormality.<sup>29</sup>

This implies that maternal deficiency of vitamin D during pregnancy affects the foetus, with known consequences on foetal growth, dentition, bone density and anthropometry.<sup>23,41</sup>

### ***Lung maturation/asthma***

Calbindin, a vitamin D dependent calcium binding protein, is a known molecular marker of 1, 25 (OH)<sub>2</sub> D<sub>3</sub> action in lung tissues. High levels of calbindin in human foetal lung tissue at 14-32 weeks of gestation, suggests that vitamin D has an important role in foetal lung development, as early as 14 weeks. Vitamin D has effect on type II pneumocytes and surfactant production also which has an impact on lung growth and development.<sup>42,43</sup>

### ***Immune system***

Immune regulatory work of vitamin D is seen in pregnancy when the adaptive immunity is reduced whereas the innate immunity is highlighted. Maternal-foetal interface is the main site of immune-regulation where placenta produces active vitamin D. Vitamin D helps in expression of placental proteins VDR which have anti-microbial and anti-inflammatory action helps in preventing infections and therefore, forms the important basis of immunomodulatory function during pregnancy.<sup>22</sup> Studies have highlighted potent effects of vitamin D on both innate and adaptive immune responses in a wide variety of tissues.<sup>24</sup> This implies that maternal level of active vitamin D must be maintained for better immune functions in child to protect from infections such as rubella simplex virus.<sup>23</sup>

### ***Congenital abnormality***

Mothers who were suffering with vitamin D deficiency during pregnancy had children with vitamin D dependent rickets. This was proved when the children were cured with subsequent administration of vitamin D 5000 IU/day.<sup>44</sup> Vitamin D is important in neuro-development vitamin D deficiency either in utero or in early life may

have adverse neuropsychiatric implications including neonatal seizure therefore becomes important to prevent it.<sup>2,22</sup>

The following discussion will elaborate on the importance of maintaining a required level of vitamin D during pregnancy for a mother.

### ***Preeclampsia***

Vitamin D is known to have effects on the blood pressure regulation in our body. A lower vitamin D level was observed in pre eclampsia compared with normal pregnancy.<sup>45</sup> Consumption of calcium-vitamin D supplements for 9 weeks during pregnancy among pregnant women at risk for pre-eclampsia resulted in decreased fasting plasma glucose and serum triglycerides levels as compared to the placebo group.<sup>12</sup>

Meta-analysis study done on 8 studies that reported odds for pre-eclampsia concluded that low (<50 nmol/l, or 20 ng/ml) serum concentration of 25 (OH) D was associated with increased risk of pre-eclampsia.<sup>46</sup> In another meta-analysis done on 15 trials showed supplementing pregnant women with vitamin D led to significantly higher levels of 25 (OH) D at term compared to placebo/control. Vitamin D supplementation, with or without calcium, is related to lower risk of preeclampsia.<sup>13</sup> A high-dose vitamin D administration of 4000 IU vitamin D among women at risk for pre-eclampsia had beneficial effects on insulin metabolism parameters, serum HDL-cholesterol.<sup>14</sup> Vitamin D supplementation reduces the risk of pre eclampsia by 48% compared to no intervention and placebo group.<sup>27</sup> The pathogenesis of preeclampsia involves a number of biological processes that may be directly or indirectly affected by vitamin D, including immune dysfunction, placental implantation, abnormal angiogenesis, excessive inflammation and hypertension.<sup>15</sup>

### ***Caesarean section***

Women who were severely vitamin D deficient [25(OH) D <37.5 nmol/l] at the time of delivery had almost 4 times the odds of caesarean birth than women who were not deficient. Vitamin D deficiency has been associated with proximal muscle weakness as well as suboptimal muscle performance and strength.<sup>9</sup>

### ***Gestational diabetes mellitus***

CYP24A1 is a cytochrome which catalyses the hydroxylation of vitamin D. This enzyme plays an important role in the vitamin D endocrine system through its regulation of the level of vitamin D. One of the most important functions of vitamin D is blood sugar regulation. CYP24A1 expression is seen to increase in GDM with a corresponding low level of vitamin D.<sup>47</sup>

It is also seen that the receptor of vitamin D are present in beta cells of pancreas highlighting its importance in blood sugar regulation.<sup>3</sup> Studies have shown that vitamin deficiency leads to insulin resistance.<sup>48</sup> All these help to understand a role of vitamin D in maintaining blood sugar and also preventing gestational diabetes mellitus.<sup>28,47,48</sup>

### NO THERE IS NO EFFECT

It would be wrong not to mention studies which have shown no major benefits of vitamin D supplementation. In one such study prenatal vitamin D deficiency and foetal and infant growth restriction, maternal vitamin D supplementation from mid pregnancy until birth or until 6 months post-partum did not improve foetal or infant growth.<sup>49</sup>

### CONCLUSION

In pregnancy these issues become critical as there are two lives to consider, one of the mother and the other of the child. Despite the lack of clear guidelines, there is sufficient evidence of benefits to suggest that you should at least consider monitoring the vitamin D status of a pregnant female. The dose of supplementation with vitamin D is not clear and needs further studies.

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### REFERENCES

- Sørensen IM, Joner G, Jennum PA, Eskild A, Torjesen PA, Stene LC. Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and risk of type 1 diabetes in the offspring. *Diabetes*. 2012;61(1):175-8.
- Hollis BW, Wagner CL. Nutritional vitamin D status during pregnancy: reasons for concern. *CMAJ*. 2006;174:1287-90.
- Kadowaki S. Vitamin D, An Issue of Endocrinology and Metabolism Clinics of North America. *J Clin Invest*. 1987;773:759-66.
- Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int*. 2009;20:1807-20.
- Sahu M, Bhatia V, Aggarwal A, Rawat V, Saxena P, Pandey A, et al. Vitamin D deficiency in rural girls and pregnant women despite abundant sunshine in northern India. *Clin Endocrinol (Oxf)*. 2009;70:680-4.
- Dasgupta A, Saikia U, Sarma D. Status of 25 (OH) D levels in pregnancy: A study from the North Eastern part of India. *Indian J Endocrinol Metab*. 2012;16:405-7.
- Specker BL. Does vitamin D during pregnancy impact offspring growth and bone? *Proc Nutr Soc*. 2012;71:38-45.
- Ota K, Dambaeva S, Han AR, Beaman K, Gilman-Sachs A, Kwak-Kim J. Vitamin D deficiency may be a risk factor for recurrent pregnancy losses by increasing cellular immunity and autoimmunity. *Hum Reprod*. 2014;29:208-19.
- Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF. Association between vitamin D deficiency and primary cesarean section. *J Clin Endocrinol Metab*. 2009;94:940-5.
- Hollis BW, Wagner CL. Vitamin D and Pregnancy: Skeletal Effects, Nonskeletal Effects, and Birth Outcomes. *Calcif Tissue Int*. 2013;92:128.
- Robinson M, Whitehouse AJ, Newnham JP, Gorman S, Jacoby P, Holt BJ, et al. Low maternal serum vitamin D during pregnancy and the risk for postpartum depression symptoms. *Arch Womens Ment Health*. 2014;17:213-9.
- Asemi Z, Tabassi Z, Heidarzadeh Z, Khorammian H, Sabihi SS, Samimi M. Effect of calcium-vitamin D supplementation on metabolic profiles in pregnant women at risk for pre-eclampsia: a randomized placebo-controlled trial. *Pak J Biol Sci*. 2012 Apr 1; 15(7):316-24.
- Cristina Palacios, Luz Maria De-Regil Lia K. Lombardo, and Juan Pablo Peña-Rosas. Vitamin D supplementation during pregnancy: Updated meta-analysis on maternal outcomes. *J Steroid Biochem Mol Biol*. 2016;164:148-55.
- Karamali M, Beihaghi E, Mohammadi AA, Asemi Z. Effects of High-Dose Vitamin D Supplementation on Metabolic Status and Pregnancy Outcomes in Pregnant Women at Risk for Pre-Eclampsia. *Horm Metab Res*. 2015;47(12):867-72.
- 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*. 2016;164:148-55.
- Hyppönen E, Cavadino A, Williams D, Fraser A, Vereczkey A, Fraser WD, et al. Vitamin D and pre-eclampsia: Original data, systematic review and meta-analysis. *Ann Nutr Metab*. 2013;63:331-40.
- Weinert LS, Reichelt AJ, Schmitt LR, Boff R, Oppermann ML, Camargo JL, et al. Serum vitamin D insufficiency is related to blood pressure in diabetic pregnancy. *Am J Hypertens*. 2014;27(10):1316-20.
- Hollis BW, Wagner CL. Vitamin D supplementation during pregnancy: Improvements in birth outcomes and complications through direct genomic alteration. *Mol Cellular Endocrinol*. 2017;453:113-30.
- Zosky GR, Hart PH, Whitehouse AJ, Kusel MM, Ang W, Foong RE, et al. Vitamin D deficiency at 16-20 weeks gestation is associated with impaired

- lung function and asthma at 6 years of age. *Ann Am Thorac Soc*. 2014;11:571–7.
20. Li W, Qin Z, Gao J, Jiang Z, Chai Y, Guan L, Ge Y, Chen Y. Vitamin D supplementation during pregnancy and the risk of wheezing in offspring: a systematic review and dose-response meta-analysis. *J Asthma*. 2018;5:1-8.
  21. Brun P, Dupret JM, Perret C, Thomasset M, Mathieu H. Vitamin D-dependent calcium-binding proteins (CaBPs) in human fetuses: comparative distribution of 9K CaBP mRNA and 28K CaBP during development. *Pediatr Res*. 1987;21(4):362-7.
  22. Eyles D, Burne T, McGrath J. Vitamin D in fetal brain development. *Semin Cell Dev Biol*. 2011;22(6):629-36.
  23. Ji Jin-Lu, Muyayalo, Kahindo, Zhang, Yonghong, Hu, et al. Immunological function of vitamin D during human pregnancy. *American J Reproductive Immunol*. 1989;78(2).
  24. Wagner CL, Taylor SN, Johnson DD, Hollis BW. The role of vitamin D in pregnancy and lactation: emerging concepts. *Womens Health (Lond)*. 2012;8(3):323-40.
  25. Hewison M. Vitamin D and immune function: an overview. *Proc Nutr Soc*. 2012;71:50–61.
  26. Bodnar LM, Klebanoff MA, Gernand AD, Platt RW, Parks WT, Catov JM, et al. Maternal vitamin D status and spontaneous preterm birth by placental histology in the US Collaborative Perinatal Project. *Am J Epidemiol*. 2014;179:168–76.
  27. De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. *Sao Paulo Med J*. 2016;134(3):274-5.
  28. Lacroix M, Battista MC, Doyon M, Houde G, Ménard J, Ardilouze JL, et al. Lower vitamin D levels at first trimester are associated with higher risk of developing gestational diabetes mellitus. *Acta Diabetol*. 2014;51:609–16.
  29. Bi WG, Nuyt AM, Weiler H, Leduc L, Santamaria C, Wei SQ. Association between Vitamin D Supplementation during Pregnancy and Offspring Growth, Morbidity, and Mortality: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2018;172(7):635-45.
  30. Dietary Reference Intakes for Vitamin D and Calcium. Food and Nutrition Board, Standing Committee in the Scientific Evaluation of Dietary References Intakes. Washington DC: National Academics Press; 2010.
  31. 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.
  32. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr*. 2008;87(4):10805-6.
  33. Nice. Antenatal care. Available at: <http://www.nice.org.uk>. Accessed on 1 January 2019.
  34. Godel JC. Position statement vitamin D supplementation: Recommendations for Canadian mothers and infants. Available at: <http://www.cps.ca/en>. Accessed on 1 January 2019.
  35. Marya RK, Rathee S, Lata V, Mudgil S. Effects of vitamin D supplementation in pregnancy. *Gynecol Obstet Invest*. 1981; 12:155–61.
  36. Marya RK, Rathee S, Manrow M. Effect of calcium and vitamin D supplementation on toxemia of pregnancy. *Gynecol Obstet Invest*. 1987;24:38–42.
  37. Mithal A, Kalra S. Vitamin D supplementation in pregnancy. *Indian J Endocrinol Metab*. 2014;18(5):593-6.
  38. Dawodu A, Saadi HF, Bekdache G, Javed Y, Altaye M, Hollis BW. Randomized controlled trial (RCT) of vitamin D supplementation in pregnancy in a population with endemic vitamin D deficiency. *J Clin Endocrinol Metab*. 2013;98:2337–46.
  39. Grant CC, Stewart AW, Scragg R, Milne T, Rowden J, Ekeroma A, et al. Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. *Pediatrics*. 2014;133:143–3.
  40. De-Regil LM, Palacios C, Ansary A, Kulier R, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev*. 2012;2:008873.
  41. Kalra P, Das V, Agarwal A, Kumar M, Ramesh V, Bhatia E, et al. Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant. *British J Nutr*. 2012;108:1052–8.
  42. Francis EC, Hinkle SN, Song Y, Rawal S, Donnelly SR, Zhu Y, et al. Longitudinal Maternal Vitamin D Status during Pregnancy Is Associated with Neonatal Anthropometric Measures. *Nutrients*. 2018;10(11):1631.
  43. Litonjua AA. Childhood asthma may be a consequence of vitamin D deficiency. *Curr Opin Allergy Clin Immunol*. 2009;9(3):202-7.
  44. Innes AM, Seshia MM, Prasad C, Al Saif S, Friesen FR, Chudley AE, et al. Congenital rickets caused by maternal vitamin D deficiency. *Paediatr Child Health*. 2002;7(7):455-8.
  45. Baker AM, Haeri S, Camargo CA Jr, Espinola JA, Stuebe AM, et al. A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia. *J Clin Endocrinol Metab*. 2010;95:5105-9.
  46. Tabesh M, Salehi-Abargouei A, Tabesh M, Esmailzadeh A. Maternal Vitamin D Status and Risk of Pre-Eclampsia: A Systematic Review and Meta-Analysis. *J Clin Endocrinol Metabolism*. 2013;98(8):3165–73.
  47. Cho GJ, Hong SC, Oh MJ, Kim HJ. Vitamin D deficiency in gestational diabetes mellitus and the role of the placenta. *Am J Obstet Gynecol*. 2013;209:560.

48. Roth J, Bonner-Weir S, Norman AW, Orci L. Immunocytochemistry of vitamin D-binding protein in chick pancreas: exclusive localization in B-cells. *Endocrinol.* 1982;110:2216-8.
49. Roth DE, Morris SK, Zlotkin S, Gernand AD, Ahmed T, Shanta SS, et al. Vitamin D Supplementation in Pregnancy and Lactation and Infant Growth. *N Engl J Med.* 2018;379 (6):535-46.

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