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MATERNAL VITAMIN D LEVELS AND ITS RELATIONSHIP WITH BIRTH WEIGHT OF NEWBORNS IN PARTURIENT WITH LATENT TUBERCULOSIS INFECTION

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ABSTRACT

Objectives: To see the relationship of maternal vitamin D levels with birthweight of neonates in pregnant females with latent tuberculosis infection

Methodology: A three arm randomized controlled trial was conducted in LTBI pregnant females. A calculated sample 99 parturient were selected and divided into three groups. As per dose of Vitamin-D supplementation participants were categorized in Group-A (No intervention/supplementation), Group-B (2000IU/day) and Group-C (4000IU/day). Vitamin D supplementation was given to the study groups as per study protocols. To maintain the safety measures throughout the study all the study participants were monitored for hypervitaminosis D. The primary outcome analysis was based on whether vitamin D supplementation has any impact on birth weight of neonates in LTBI pregnant females. Improvement in fetal vitamin D levels after supplementation was assessed as our secondary outcome. At the end of the study period, a total of 90 patients were available for follow up with an overall attrition of (n=9); four from Group-A, three from Group-B and two from Group-C.

Results: Mean age of our study participants was 29±3.6 years. 44 (48.8%) participants were having BMI ≥ 25 kg/m^2 while remaining were having BMI <25 kg/m^2. There were only 14 (15.5%) participants that were having sufficient vitamin D levels, 23 (25.5%) participants were having insufficient Vitamin D levels and 53 (59%) were found deficient for vitamin D levels. An overall 85.8% (85/99) participants were having VD levels < 30ng/dl. Out of total 90 deliveries 21 (23.3%) participants delivered LBW babies. 15 females were from the group that was not receiving any supplementation, 04 females were from the group receiving 2000IU/day of VD and only 01 from the group receiving 4000IU/day supplements. The association was significantly reduced with supplementation of Vitamin-D as p-value <0.001. A positive correlation was found between maternal vitamin D and birthweight of newborn ($\rho = 0.691$ with $p < 0.001$)

Conclusions: A significant relationship exists between maternal vitamin D levels and birthweight of neonates. Taking Vitamin D by LTBI pregnant women is effective to decrease the incidence of low birth weight.

Keywords: Birth weight, Maternal and Child Health, Latent TB, Pregnancy Outcomes, Vitamin D

INTRODUCTION

Vitamin D deficiency (VDD) is common in all age groups, with women of reproductive age being particularly susceptible to it.[1] It is considered a deficiency when serum 25(OH)D levels drop below 20 ng/mL. Several widespread epidemiological studies have conclusively connected VDD during pregnancy to higher odds for many pregnancy problems such as neonatal birth weight.[2,3] Low birth weight by WHO definition is the weight of the child below 2500 grams.[4] The average prevalence of preterm birth is about 11% globally whereas that for low birth weight is around 14.6%.[5, 6] Various studies have investigated the relationship between gestational VDD, preterm delivery and low birth weight, although the results are inconclusive with researchers' opinions varying on this point.[7, 8] As per the World Health Organization, women suffering from VDD should take Vitamin D supplements on a daily basis not exceeding 200 IU (5 µg). Nevertheless, WHO has not offered any advice to expectant mothers on how they can use Vitamin D to ensure better health of their children or themselves.[9] In various parts of high prevalence of VDD particularly in low and middle income countries it is common for women to be advised about taking Vitamin D as a supplement which can help minimize the occurrence of VDD and promote general wellbeing among them.[1] However, WHO expressed its concern with regard to risk in terms vitamin D causing low birth weight and premature delivery.[9] Due to its importance in cell proliferation,differentiation and maturation processes during fetal development,vitamin D is known to be a critical factor.[10]

Randomized controlled trials (RCTs) have also demonstrated that Vitamin D supplementation is also important in order to prevent poor neonatal outcomes which emphasizes the need to solve VDD in expectant mothers so as to improve maternal and fetal health.[11] Similarly, studies have demonstrated an association between gestational VDD and delivery of small-for-gestational-age infants who are LBW.[12] This underscores the importance of addressing VDD during pregnancy for better neonatal health. It has been long accepted that reduced levels of cholecalciferol in the blood stream lead to weak immunity and high tuberculosis risk.[13] Several studies have indicated that inadequate vitamin D3 levels are associated with increased susceptibility to active tuberculosis.[14-18] While the deficiency of cholicalifeorl levels in blood is common among all ages,[19] very few studies have looked at how often vitamin D insufficiency is in people with LTBI.[20,21] So we aimed to determine the relationship between maternal vitamin D level and birth weight of neonates among pregnant females with latent tuberculosis infection
vitamin D levels with birthweight of neonates in pregnant females with latent tuberculosis infection

MATERIALS AND METHODS

Study Design & Setting: A three arm (parallel) randomized controlled trial was conducted in a tertiary care health facility in Lahore

Sample Size: The size of the subject sample for the study was calculated based on the anticipated effect size of vitamin D supplementation on adverse fetomaternal outcomes, statistical power, and significance level. For 90% power of study and 5% margin of error (a = 0.05), there has to be a statistically significant increase in D3 by 10 ng/ml [22], at least 30 patients per arm were needed. The calculation was based on the assumption of a low correlation between baseline and final readings, as well as an estimated standard deviation of approximately 10 for 25(OH)D measurements at a single time point. By adding 10% loss to follow ups, because of either

withdrawal from participation or termination of care, the calculated sample size was 33 in each group, hence a total of 99 participants were recruited.

Sample Selection: Pregnant females with age from 18-35 years, already enrolled for antenatal care in the specified setting coming regularly for prenatal checkups, having latent tuberculosis infection confirmed by tuberculin skin test as per protocols were included in this study. Female having history of active TB disease, any immunocompromised state (like HIV) and/or currently taking immunosuppressors, anticonvulsants, or antimycobacterial (tuberculosis) drugs. During the month before enrollment, taking any dietary supplement providing more than 400 IU (10 mcg) of vitamin D daily; A complex medical or obstetric history; alternatively, a history of significant congenital anomalies, birth asphyxia, or perinatal deaths reported during the baby's delivery were excluded from study.

Interventions: The randomization sequence allocated participants into three groups

- **Group-A:** Non interventional (control) group: Participants in this group will not receive any vitamin D supplementation
- **Group-B:** Participants receiving a daily dose of 2000 IU/day
- **Group-C:** Participants receiving a daily dose of 4000 IU/day

The intervention groups (B & C) received oral supplementation of Vitamin D at a dosage of 2000 IU per day and 4000 IU per day, in addition to standard antenatal care. The control group received standard antenatal care. All groups continued their assigned intervention until delivery.

Data Collection and Monitoring: Trained research staff collected the data on outcome measures using standardized data collection forms and instruments. In order to guarantee data validity, completeness, and consistency, regular monitoring and quality control procedures were carried out. Data collection encompassed baseline assessments, antenatal visits, medical record reviews, and postnatal follow-up. Data were collected using structured data collection forms and electronic databases. Trained research staff ensured the completeness and accuracy of data collection, with regular quality checks implemented throughout the study period.

Study Drop outs: At the end of the study period, a total of 90 patients were available for follow up with an overall attrition of (n=9); four from Group-A, three from Group-B and two from Group-C.

Data Analysis: Data analysis was conducted using appropriate statistical methods, including intention-to-treat analysis. Continuous variables underwent analysis using t-tests or non-parametric tests as appropriate, while categorical variables were assessed utilizing chi-square tests or Fisher's exact tests. Subgroup analyses and sensitivity analyses were conducted to investigate potential effect modifiers and sources of heterogeneity, enhancing the depth of understanding regarding the impact of variables on the study outcomes. These analyses help identify any subgroup-specific effects or variations in treatment effects across different subpopulations, thus providing valuable insights into the factors influencing the study results. Correlation analysis was performed to see the relationship of maternal vitamin-D levels and birth weight of neonates. P value ≤ 0.05 was considered as significant

Ethical Consideration: Prior to enrollment, informed consent was obtained from all participants, emphasizing confidentiality and voluntary participation throughout the study duration. This process ensured that participants were fully aware of the study's objectives, procedures, and potential risks, and that their personal information would be protected.The research protocol, informed consent documents, data collection procedures, and study materials were reviewed for compliance with ethical standards and regulations.

The article was extracted from doctoral thesis entitled "Impact of Vitamin D Supplementation on Fetomaternal Outcomes in Pregnant Females with Latent Tuberculosis Infection: A Randomized Controlled Trial in Lahore-Pakistan" of first/corresponding author (UJI) whose ethical approval was acquired from the Institutional Review Board of Punjab University, documented under letter number D/185/FIMS.

RESULTS

Mean age of our study participants was 29±3.6 years. 44 (48.8%) participants were having BMI ≥ 25 kg/m^2 while remaining were having BMI <25 kg/m^2. There were only 14 (15.5%) participants that were having sufficient vitamin D levels, 23 (25.5%) participants were having insufficient Vitamin D levels and 53 (59%) were found deficient for vitamin D levels as shown inTable-01.

An overall 85.8% (85/99) participants were having VD levels < 30ng/dl. Table-02 shows measures of birth weight of neonates with respect to various study groups. Out of total 90 deliveries 21 (23.3%) participants delivered LBW babies. 15 females were from the group that was not receiving any supplementation, 04 females were from the group receiving 2000IU/day of VD and only 01 from the group receiving 4000IU/day supplements. The association was significantly reduced with supplementation of Vitamin-D as p-value <0.001.

Table 01: Baseline Characteristics of Study Participants

	Group-A (No Intervention) n=29	***Group-B (2000IU/day) n=30***	***Group-C (4000IU/day) n=31***
***Age** in years (mean ± SD)*	27.6±3.0	29.1±4.2	30.2±3.1
BMI			
<25kg/m^2	16 (55%)	16 (53.3%)	14 (45%)
≥ 25 kg/m^2	13 (45%)	14 (46.7)	17 (55%)
***Calcium levels** (ng/dl)* [a]	8.53±0.36	8.57±0.32	8.40±0.26
***Vitamin-D levels** (ng/dl)* [b]	19.46±5.43	21.5±5.43	17.8±8.51
Vitamin-D Sufficiency [c]			
Sufficient n (%)	04 (13.8%)	05 (16.7%)	05 (16.1%)
Insufficient n (%)	08 (27.6%)	07 (22.8%)	08 (27.6%)
Deficient n (%)	17 (58.6%)	17 (56.7%)	19 (61.3%)

a Maternal baseline calcium levels presented as mean ± S.D

b Maternal baseline Vitamin-D levels presented as mean ± S.D

c Sufficiency was declared if serum Vitamin-D levels ≥ 30ng/dl, Insufficiency if levels 20-29ng/dl, deficiency if <20 ng/dl

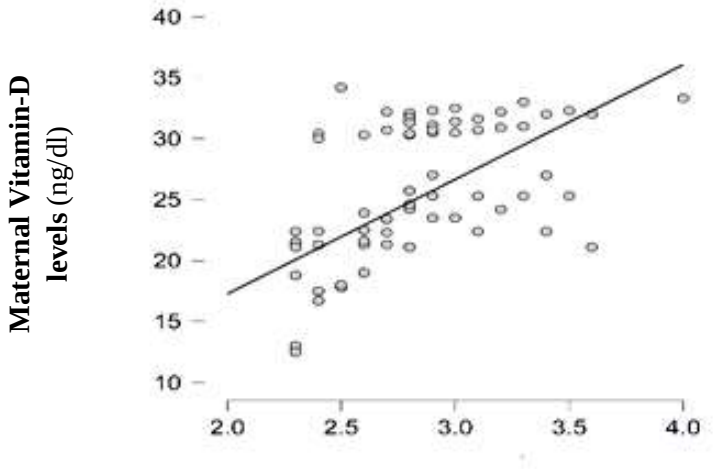
Table 02: Measures of Fetal Outcome: Birth Weight

	Group-A (n=29) No Intervention n(%)	***Group-B (n=30) 2000IU/day n(%)***	***Group-C (n=31) 4000IU/day n(%)***	***Total (n=90) n (%)***
LBW [a]	15 (51.7)	04 (13.3%)	01 (3.2%)	21 (23.3%)
NBW [b]	14 (48.3%)	25 (83.3%)	30 (96.8%)	69 (76.7%)
				p-value < 0.001

a Neonates weighing <2.5 kg on birth presented as n(%)

b Neonates weighing ≥2.5 kg on birth presented as n(%)

Figure-01: Correlation of Maternal Vitamin D Levels with Birth Weight



There was a positive correlation between maternal vitamin D and birthweight of newborn ($\rho = 0.691$ with $p < 0.001$) as shown in Figure-01.

DISCUSSION

This study addresses a significant knowledge gap, as there is limited research on the impact of maternal vitamin D deficiency on neonatal birth weight. Our findings align with previous studies [23, 24] and suggest a link between maternal vitamin D deficiency and low birth weight, particularly when vitamin D levels are measured using ELISA (Enzyme-Linked Immunosorbent Assay). The development and growth of a fetus rely heavily on vitamin D, and this research stresses the importance of mothers maintaining adequate levels of this essential nutrient to ensure a healthy birth outcome. Since the fetus is in a critical phase of rapid growth and development, it is particularly vulnerable to the negative effects of vitamin D deficiency, making sufficient maternal vitamin D levels crucial for supporting the baby's growth and development.[25] Research has consistently shown that a lack of sufficient vitamin D in pregnant women is a significant risk factor for restricted fetal growth, independent of other potential factors.[26, 27] Maternal vitamin D deficiency has a well-established impact on calcium absorption and bone metabolism, which in turn reduces fetal bone growth. According to Mahon et al [28] vitamin D deficiency in mothers increases the risk of low birth weight (LBW) in fetuses, as it disrupts fetal femoral development and hinders proper bone formation. Additionally, maternal vitamin D levels influence fetal weight by modulating the immune response at the interface between the fetus and mother. Adequate vitamin D levels enhance the production of antimicrobial peptides, which help fight infections, by increasing vitamin D receptor levels and activating the toll-like receptor pathway. In contrast, vitamin D deficiency can weaken this immune response, making the fetus more vulnerable to infections and potentially impacting fetal growth.[29] Grether et al [30] found that vitamin D deficiency in pregnant women leads to placental chorioamnionitis, which disrupts placental blood supply, impairs normal fetal growth, and increases the risk of low birth weight. Furthermore, vitamin D and its derivatives play a crucial role in regulating various hormones that influence glucose and fatty acid metabolism, ultimately affecting the supply of nutrients to the fetus. Notably, research has established a link between vitamin D levels and insulin-like growth factor-1 (IGF-1) concentration, highlighting the importance of vitamin D in supporting fetal growth and development.[31] Vitamin D supplements have been shown to increase IGF-1 concentration[32]; whereas vitamin D deficiency during pregnancy can limit intrauterine growth by downregulating IGF-1 concentration.[33] Additionally, vitamin D deficiency is associated with an increased risk of small for gestational age (SGA) and intrauterine growth restriction (IUGR), which are characterized by a birth weight below 2500g.

SGA infants are born smaller than normal for their gestational age, typically defined as a weight below the 10th percentile for their corresponding gestational age.[33-35] The outcome of the current trial was to examine the adverse fetal outcomes in vitamin D-deficient LTBI-positive mothers. It was observed that the average rate of change in cholecalciferol concentrations throughout gestation was correlated with fetal outcomes. This suggests that the trajectory of maternal vitamin D levels during pregnancy may influence fetal health and development. The rates of LBW was 17%. Preterm birth and LBW had an average prevalence of 11% and 14.6% worldwide, respectively.[5,6] whereas 32.5 million births were LBW.[36] The causes of these results are believed to be complex and have not been completely determined.[37,38]

A study conducted in 2022 showed that pregnancy-related vitamin D augmentation increased infant vitamin D levels considerably, reduced the number of LBW babies, and enhanced APGAR ratings. The mother's cholecalciferol level in blood bloodstream was the most distinguished predictor of the amount of vitamin D in the cord blood. Newborns whose mothers had insufficient levels of vitamin D were found to be five times more likely to have decreased concentrations of cholecalciferol in their cord blood. Maternal hypovitaminosis D was significantly associated with birth weight and preterm delivery, indicating its impact on fetal development and gestational outcomes. Additionally, a trend towards a higher risk of live birth, sick gestation syndrome in neonates, perinatal depression, and neonatal hyperbilirubinemia was observed among expectant mothers with hypovitaminosis D. These findings highlight the substantial health risks posed by maternal vitamin D deficiency, affecting both the unborn child and the mother herself.[39] There is an unambiguous connection between cholecalciferol and the likelihood of preterm birth in all trimesters. A direct correlation was found between the change in D3 levels during antenatal period and BW z-scores and low birth weight.[40] Pregnant mothers who are vitamin D3 deficient have significantly adverse neonatal outcomes.[41]

A review revealed that females with serum conc. Of cholecalciferol below 30 nmol/L were more likely to have low birth weight (LBW) babies and were at a higher risk of delivering infants classified as small for gestational age compared to those with recommended vitamin D levels, which are above 75 nmol/L. Additionally, it was found that compared to females with vitamin D concentrations above 75 nmol/L, women with levels below 50 nmol/L had higher odds of experiencing premature birth.[42] Diminished vitamin D status in mothers, as indicated by serum D3 levels $\leq$20 ng/ml, has emerged as a significant risk factor for adverse fetal consequences, including underdevelopment at birth, prematurity, and an increased likelihood of children developing osteoporosis and dental issues later in life. These findings underscore the critical importance of maintaining adequate cholecalciferol levels during gestation to promote optimal maternal and fetal health outcomes. Ensuring sufficient vitamin D intake and monitoring maternal cholecalciferol status throughout gestation can help mitigate these risks and support healthy fetal development and long-term well-being.[43-46]

Furthermore, a study conducted in 2015 observed that infants born to females who took supplements that contain D3 exhibited noticeably greater size and weight at birth.[47] Improving low serum cholecalciferol status during the gestational period may enhance mother weight gain and fetal development indices.[48] In a local trial, vitamin D supplementation increased the vitamin D status of the mother and the newborn, as well as the newborn's outcomes in terms of head circumference, BW, length, and Apgar scores.[49]

CONCLUSION

A significant relationship exists between maternal vitamin D levels and birthweight of neonates. Taking Vitamin D by LTBI pregnant women is effective to decrease the incidence of low birth weight.

REFERENCES

1. Roth, D.E., et al., *Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low-and middle-income countries*. 2018, Wiley Online Library.
2. Amegah, A.K., M.K. Klevor, and C.L. Wagner, *Maternal vitamin D insufficiency and risk of adverse pregnancy and birth outcomes: a systematic review and meta-analysis of longitudinal studies.* PLoS One, 2017. **12**(3): p. e0173605.
3. Vivanti, A.J., et al., *Vitamin D and pregnancy outcomes: Overall results of the FEPED study.* Journal of Gynecology Obstetrics and Human Reproduction, 2020. **49**(8): p. 101883.
4. Berglund, S.K., et al., *Effects of iron supplementation of LBW infants on cognition and behavior at 3 years.* Pediatrics, 2013. **131**(1): p. 47-55.
5. Chawanpaiboon, S., et al., *Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis.* The Lancet global health, 2019. **7**(1): p. e37-e46.
6. Blencowe, H., et al., *National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis.* The Lancet global health, 2019. **7**(7): p. e849-e860.
7. Thorp, J., et al., *Vitamin D status and recurrent preterm birth: a nested case–control study in high-risk women.* BJOG: An International Journal of Obstetrics & Gynaecology, 2012. **119**(13): p. 1617-1623.
8. Miliku, K., et al., *Maternal vitamin D concentrations during pregnancy, fetal growth patterns, and risks of adverse birth outcomes.* The American journal of clinical nutrition, 2016. **103**(6): p. 1514-1522.
9. Organization, W.H., *WHO recommendations on antenatal care for a positive pregnancy experience: screening, diagnosis and treatment of tuberculosis disease in pregnant women. Evidence-to-action brief: Highlights and key messages from the World Health Organization's 2016 global recommendations*. 2023: World Health Organization.
10. Gale, C.R., et al., *Maternal vitamin D status during pregnancy and child outcomes.* European journal of clinical nutrition, 2008. **62**(1): p. 68-77.
11. Hollis, B.W. and C.L. Wagner, *Vitamin D and pregnancy: skeletal effects, nonskeletal effects, and birth outcomes.* Calcified tissue international, 2013. **92**: p. 128-139.
12. Chen, Y.-H., et al., *Maternal vitamin D deficiency during pregnancy elevates the risks of small for gestational age and low birth weight infants in Chinese population.* The Journal of Clinical Endocrinology & Metabolism, 2015. **100**(5): p. 1912-1919.
13. Tung, Y., T. Ou, and W. Tsai, *Defective Mycobacterium tuberculosis antigen presentation by monocytes from tuberculosis patients.* The International journal of tuberculosis and lung disease, 2013. **17**(9): p. 1229-1234.
14. Ho-Pham, L.T., et al., *Association between vitamin D insufficiency and tuberculosis in a Vietnamese population.* BMC infectious diseases, 2010. **10**: p. 1-8.
15. Kim, J.H., et al., *Low serum 25-hydroxyvitamin D level: an independent risk factor for tuberculosis?* Clinical nutrition, 2014. **33**(6): p. 1081-1086.
16. Arnedo-Pena, A., et al., *Vitamin D status and incidence of tuberculosis infection conversion in contacts of pulmonary tuberculosis patients: a prospective cohort study.* Epidemiology & Infection, 2015. **143**(8): p. 1731-1741.
17. Huang, S.-J., et al., *Vitamin D deficiency and the risk of tuberculosis: a meta-analysis.* Drug design, development and therapy, 2016: p. 91-102.
18. Zeng, J., et al., *A serum vitamin D level< 25nmol/l pose high tuberculosis risk: a meta-analysis.* PloS one, 2015. **10**(5): p. e0126014.
19. Holick, M.F., et al., *Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline.* The Journal of clinical endocrinology & metabolism, 2011. **96**(7): p. 1911-1930.

20. Arnedo-Pena, A., et al., *Latent tuberculosis infection, tuberculin skin test and vitamin D status in contacts of tuberculosis patients: a cross-sectional and case-control study.* BMC infectious diseases, 2011. **11**(1): p. 1-8.
21. Wingfield, T., et al., *The seasonality of tuberculosis, sunlight, vitamin D, and household crowding.* The Journal of infectious diseases, 2014. **210**(5): p. 774-783.
22. Mir, S.A., et al., *Efficacy and safety of Vitamin D supplementation during pregnancy: A randomized trial of two different levels of dosing on maternal and neonatal Vitamin D outcome.* Indian journal of endocrinology and metabolism, 2016. **20**(3): p. 337.
23. Davies, T.F., L.M. Sachs, and M.A. Campinho, *OPEN ACCESS EDITED AND REVIEWED BY.* The Role of Thyroid Hormones in Vertebrate Development, volume II, 2024: p. 4.
24. Abdolrazaghnejad, A., et al., *Relationship between vitamin D level and preterm labor in pregnant women in Zahedan, Iran.* Fertility, Gynecology and Andrology, 2022. **2**(1).
25. Kanike, N., N. Kannekanti, and J. Camacho, *Vitamin D Deficiency in Pregnant Women and Newborn.* Vitamin D, 2021.
26. Wang, H., et al., *Maternal early pregnancy vitamin D status in relation to low birth weight and small-for-gestational-age offspring.* The Journal of steroid biochemistry and molecular biology, 2018. **175**: p. 146-150.
27. Fang, K., et al., *Maternal vitamin D deficiency during pregnancy and low birth weight: a systematic review and meta-analysis.* The Journal of Maternal-Fetal & Neonatal Medicine, 2021. **34**(7): p. 1167-1173.
28. Mahon, P., et al., *Low maternal vitamin D status and fetal bone development: cohort study.* Journal of Bone and Mineral Research, 2010. **25**(1): p. 14-19.
29. Qin, L.-L., et al., *Does maternal vitamin D deficiency increase the risk of preterm birth: a meta-analysis of observational studies.* Nutrients, 2016. **8**(5): p. 301.
30. Grether, J.K., et al., *Prenatal and perinatal factors and cerebral palsy in very low birth weight infants.* The Journal of pediatrics, 1996. **128**(3): p. 407-414.
31. Bogazzi, F., et al., *Vitamin D status may contribute to serum insulin-like growth factor I concentrations in healthy subjects.* Journal of endocrinological investigation, 2011. **34**: p. e200-e203.
32. Ameri, P., et al., *Vitamin D increases circulating IGF1 in adults: potential implication for the treatment of GH deficiency.* European journal of endocrinology, 2013. **169**(6): p. 767-772.
33. Woitge, H.W. and B.E. Kream, *Calvariae from fetal mice with a disrupted Igf1 gene have reduced rates of collagen synthesis but maintain responsiveness to glucocorticoids.* Journal of Bone and Mineral Research, 2000. **15**(10): p. 1956-1964.
34. Kajdy, A., et al., *Development of birth weight for gestational age charts and comparison with currently used charts: defining growth in the Polish population.* The Journal of Maternal-Fetal & Neonatal Medicine, 2021. **34**(18): p. 2977-2984.
35. Hoftiezer, L., et al., *Defining small-for-gestational-age: prescriptive versus descriptive birthweight standards.* European journal of pediatrics, 2016. **175**: p. 1047-1057.
36. Lee, A.C., et al., *National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010.* The Lancet global health, 2013. **1**(1): p. e26-e36.
37. Frey, H.A. and M.A. Klebanoff. *The epidemiology, etiology, and costs of preterm birth*. in *Seminars in fetal and neonatal medicine*. 2016. Elsevier.
38. McCowan, L. and R.P. Horgan, *Risk factors for small for gestational age infants.* Best practice & research clinical obstetrics & gynaecology, 2009. **23**(6): p. 779-793.
39. Gowtham, T., et al., *Impact of maternal hypovitaminosis D on birth and neonatal outcome–a prospective cohort study.* The Journal of Maternal-Fetal & Neonatal Medicine, 2022. **35**(25): p. 9940-9947.
40. Benaim, C., et al., *Vitamin D during pregnancy and its association with birth outcomes: a Brazilian cohort study.* European Journal of Clinical Nutrition, 2021. **75**(3): p. 489-500.

41. Noamam, K.H. and T.N. Abdulla, *Relationship of Low Maternal Vitamin D3 Level and Adverse Early Neonatal Outcomes.* Indian Journal of Forensic Medicine & Toxicology, 2021. **15**(1): p. 1197-1204.
42. Tous, M., et al., *Vitamin D status during pregnancy and offspring outcomes: a systematic review and meta-analysis of observational studies.* European journal of clinical nutrition, 2020. **74**(1): p. 36-53.
43. Karras, S.N., et al., *Maternal vitamin D levels during pregnancy and neonatal health: evidence to date and clinical implications.* Therapeutic advances in musculoskeletal disease, 2016. **8**(4): p. 124-135.
44. McAree, T., et al., *Vitamin D deficiency in pregnancy–still a public health issue.* Maternal & child nutrition, 2013. **9**(1): p. 23-30.
45. Weinert, L.S. and S.P. Silveiro, *Maternal–fetal impact of vitamin D deficiency: a critical review.* Maternal and child health journal, 2015. **19**: p. 94-101.
46. Wagner, C., et al., *Post-hoc comparison of vitamin D status at three timepoints during pregnancy demonstrates lower risk of preterm birth with higher vitamin D closer to delivery.* The Journal of steroid biochemistry and molecular biology, 2015. **148**: p. 256-260.
47. Pérez-López, F.R., et al., *Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials.* Fertility and sterility, 2015. **103**(5): p. 1278-1288. e4.
48. Hashemipour, S., et al., *Effect of treatment of vitamin D deficiency and insufficiency during pregnancy on fetal growth indices and maternal weight gain: a randomized clinical trial.* European Journal of Obstetrics & Gynecology and Reproductive Biology, 2014. **172**: p. 15-19.
49. Hossain, N., et al., *Obstetric and neonatal outcomes of maternal vitamin D supplementation: results of an open-label, randomized controlled trial of antenatal vitamin D supplementation in Pakistani women.* The Journal of Clinical Endocrinology & Metabolism, 2014. **99**(7): p. 2448-2455.