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Maternal vitamin D deficiency and GDM risk: evidence for the case of investing more attention in antenatal clinics

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Gestational diabetes mellitus (GDM) is a global public health problem, and in India, it affects about 20 % of pregnancies. India, despite being a tropical country with abundant sunshine has a high prevalence (80 %) of vitamin D deficiency (VDD) among reproductive-aged women. Global and Indian evidence links VDD with a higher risk of hyperglycaemia in pregnancy and GDM. VDD has also been implicated in gestational hypertension, preterm birth and poorer offspring health. Global scientific consensus acknowledges the need for maternal vitamin D screening and supplementation, but knowledge gaps exist about optimal blood levels (50–100 nmol/l), and the required vitamin D dosage (400–4000 IU). Diet can provide <10 % of the vitamin D requirements, food fortification can deliver limited amounts, and hence optimal antenatal supplementation is key. Prenatal calcium supplements containing 400 IU of vitamin D may be sufficient for calcium absorption and bone health, but may not provide immunomodulatory benefits, including GDM prevention. Increasing evidence calls for higher maternal vitamin D requirements (2000–4000 IU) for skeletal, metabolic and immune health benefits. Current screening and supplementation for maternal VDD in India is low. We need to invest in future studies to determine optimal maternal vitamin D requirements and formulate policies for vitamin D supplementation to prevent GDM. Improving the maternal vitamin D status is an important nutritional priority for policymakers to reduce the large economic burden of non-communicable diseases (10 % of India's gross domestic product), and eventually achieve the 2030 UN sustainable development goals.

Key words: Vitamin D: India: Gestational diabetes mellitus: Supplementation: Policy and review

Gestational diabetes mellitus (GDM) is any degree of glucose intolerance with onset or first recognition during pregnancy that is not clearly overt diabetes[1]. GDM causes many adverse health consequences for both a mother and her children[2]. In the short-term, GDM increases the risk of obstructed labour and increased rates of instrumental and caesarean deliveries in the mother[3], and in the baby, GDM increases the risk of macrosomia, shoulder dystocia, respiratory distress syndrome, congenital heart abnormalities, preterm birth and fetal death[4]. Additionally, GDM may reduce blood flow to the umbilical artery leading to poor fetal growth[5]. The biggest long-term consequence of GDM is intrauterine programming of insulin resistance which contributes to increased adiposity and a higher risk of type 2 diabetes mellitus in the offspring[6].

GDM is a global public health problem, and in India, it affects about 20 % of pregnancies[7]. The women in India

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; GDM, gestational diabetes mellitus; VDD, vitamin D deficiency.

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GDM strategy predicted that more than 60 and 90 % of GDM women will develop type 2 diabetes mellitus in the next 5 and 10 years, respectively[8]. Nutritional factors are increasingly being recognised as important modifiable risk factors to prevent GDM, among which improving the vitamin D status of reproductive-aged women may be a potential strategy to prevent hyperglycaemia in pregnancy and GDM[9–12]. Vitamin D deficiency (VDD) affects 70–80 % of reproductive-aged women in India[11].

The aim of the current review is to summarise the evidence linking VDD and GDM risk, to make a case for investing to improve the vitamin D status of reproductive-aged women in India. Therefore, the review will summarise the evidence of VDD prevalence in India, the importance of vitamin D for maternal and child health, evidence comprising of observational, intervention and mechanistic studies linking VDD and GDM, requirements of vitamin D and feasible approaches to prevent maternal VDD and the rationale for investing in education, research, screening and supplementation of vitamin D in antenatal clinics to prevent GDM.

Vitamin D deficiency in India

Vitamin D is produced when skin is exposed to sunlight's UV B radiation of wavelength 290–320 nm, to convert 7-dihydrocholesterol in the skin to previtamin D3, which is released into the bloodstream, along with the vitamin D binding protein[13]. Previtamin D3 undergoes activation in the liver and kidneys to produce the 25-hydroxyvitamin D [25(OH)D][9]. Cellular receptors for the active form of vitamin D [25(OH)D] known as vitamin D receptors are found in the intestine, bones and nearly every tissue in the human body[9–12].

India, despite being a tropical country, situated between 8·4 and 34·7 degrees' north latitude geographically and getting adequate sunshine round the year, there is widespread prevalence of VDD in the Indian population in all age groups[11,13]. Prevalence of VDD ranges between 70 and 100 % affecting all, from 'children to elderly' from 'urban to rural' and from 'planes to hills' across the country[14,15]. Indian data indicate that VDD is prevalent in 70–80 % of adolescents and reproductive-aged women including pregnant and lactating mothers[14,16]. Some of the causes for the rampant VDD in healthy individuals include the presence of higher melanin pigment in skin, low intake of vitamin D and calcium-rich foods, limited availability and intake of vitamin D fortified foods, increasing sedentary and indoor lifestyles due to urbanisation, high rise buildings, increasing pollution that inhibits the synthesis of vitamin D, use of air conditioning and sunscreen, cultural practices of covering oneself with a veil (e.g. purdah and burqa) and sun avoidance due to a cultural desire for fair skin[13,15].

Vitamin D in maternal and child health

The importance of vitamin D during pregnancy is known, as demonstrated by physiologically higher levels of 1,25-dehydroxy vitamin D seen in the second and third trimesters[9,17]. The fetus accrues about 250 mg of calcium daily, due to greater calcium requirements and its absorption. The placenta expresses vitamin D receptors to activate 25(OH)D from the previtamin D3, similar to the kidneys[17,18]. An elevation of three to four times in circulating $1,25(OH)_2D$ levels, the substrate of 25(OH)D, occurs during pregnancy due to an increase in the serum vitamin D binding protein that controls the amount of 'free' $1,25(OH)_2D$ available in the circulation[19]. This process may be driven by the placenta, calcium and phosphorous balance, and the homeostasis of calcitonin, prolactin and parathyroid hormones[20].

Long-standing VDD is a risk factor for the development of osteopenia and osteoporosis in the mother[11]. Skeletal manifestation of maternal VDD is well established and can lead to weakened fetal bone ossification and neonatal hypocalcaemia, tetany, rickets and osteomalacia in the growing child[17]. Evidence is also accumulating on the potential benefits of a higher maternal vitamin D status in the development of the fetal immune, pancreatic, metabolic, cardiovascular and neural systems[11,21].

Global and local evidence links VDD with an increased risk of GDM and hypertension, pre-eclampsia, preterm birth, caesarean deliveries and postpartum depression. Maternal VDD is also associated with poorer offspring health in the short and long term, including reduced growth, delayed milestones, lower bone mineralisation, asthma and impaired cognition[10,22].

Evidence linking maternal vitamin D deficiency, hyperglycaemia and GDM

Observational evidence

Global and local observational evidence suggests a link between VDD and a higher GDM risk. A systematic review of eighty-seven observational studies (*n* 55 859) and twenty-five randomised controlled trials (*n* 2445) found that lower vitamin D status during pregnancy was associated with a higher GDM risk (OR 1·85, 95 % CI 1·47, 2·32)[12]. Similarly, two other meta-analyses of observational studies also indicated that women with VDD had 40–60 % higher risk of GDM (mean 25(OH)D levels were 3·9 and 7·4 nmol/l in GDM *v.* non-GDM women, respectively)[23,24].

In Bangalore, South India, women in the lowest quartile (*n* 392) of plasma 25(OH)D levels during their early pregnancy, compared to other quartiles, had a higher GDM risk (OR 2·32, 95 % CI 1·10, 4·91)[25]. Another retrospective study in Mysore, South India (*n* 559), reported that serum 25(OH)D levels were not associated with GDM, but were inversely associated with 30 min glucose concentrations ($P = 0·03$) and higher fasting proinsulin levels ($P = 0·04$)[26].

Intervention studies

Whilst good quality observational evidence shows that lower vitamin D status is associated with a higher

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GDM risk, intervention studies have not clearly demonstrated a causal role of vitamin D in preventing GDM[27]. A Cochrane meta-analysis including two studies that compared vitamin D supplementation during pregnancy with placebo found no difference in the risk of GDM[28]. In contrast, another meta-analysis (*n* 2643) showed that vitamin D supplementation reduced GDM risk (RR 0·61, 95 % CI 0·34, 0·83) with all trials included, but showed no effect when rigorous eligibility criteria were applied[29]. Although intervention studies have not clearly demonstrated an effect of GDM reduction, many studies indicate that a daily dose of 4000 IU of vitamin D supplementation improved the maternal and neonatal 25(OH)D levels[20,29–38]. There are sparse data on intervention studies in India to support the beneficial effect of maternal vitamin D supplementation on the lower risk of GDM[39]. Evidence acknowledges that the degree of rise in the 25(OH)D levels varied between individuals in many intervention studies[20,27,32]. Assessment of outcomes between various trials is complex due to the differences in the daily vitamin D doses administered (ranging from 200 to 4000 IU), and the timing of supplementation during pregnancy[10,27]. An important reason for intervention studies showing conflicting results could be that most studies initiated vitamin D supplementation during mid or late pregnancy, after the critical developmental periods of placentogenesis and embryogenesis, and hence could not show a significant effect in GDM reduction[10].

Possible mechanisms

Vitamin D's role to prevent GDM may be biologically plausible. Laboratory studies show that vitamin D may influence glucose homeostasis by increasing insulin sensitivity in the liver, muscle and adipose tissue by stimulating the expression of insulin receptors thus regulating glucose uptake[40]. Vitamin D also may improve glucose uptake by stimulating nuclear vitamin D receptors which up-regulate GLUT-4 production and function. Insulin secretion may be enabled by vitamin D's role in up-regulating ca-dependent insulin secretion via regulating extra and intracellular calcium pools. Vitamin D's anti-inflammatory action may down-regulate cytokine production from macrophages and protects β-cell from destruction[41].

Vitamin D requirements

There is considerable global debate regarding vitamin D requirements during pregnancy. The Indian Council of Medical Research recommends 400–600 IU of vitamin D[42]. The National Institute for Health and Clinical Excellence in the UK, based on the Scientific Advisory Committee on Nutrition guidelines recommend a vitamin D intake of 400 IU[43]. The Institute of Medicine and the European Nutrition Societies recommend a daily dose of 600 IU of vitamin D for adults and the elderly[44,45]. Most of these recommendations are based on the principle that a vitamin D intake of 400–600 IU/d would suffice to attain a circulating 25(OH)D level of 50 nmol/ml[44].

The International Osteoporosis Foundation recommends higher daily intakes of vitamin D of 800–1000 IU for people at risk of osteoporosis and 2000 IU for populations who have obesity or who are vitamin D deficient or those who have limited sun exposure[46]. The Endocrine Society recommends a vitamin D intake of 1500–2000 IU/d to achieve a circulating 25(OH)D level of >75 nmol/l, and an upper safe limit of 10 000 IU/d for pregnant women at the risk of VDD[47]. The higher vitamin D recommendations are based on some evidence which point that the 25(OH)D thresholds of >50 nmol/l as sufficiency may be less applicable to pregnancy, when the 25(OH)D formation from its substrate $1,25(OH)_2D$ may be best achieved at a circulating 25 (OH)D level of 80–100 nmol/l[10]. The higher 25(OH)D level of 80–100 nmol/l required for optimal calcium absorption, bone mineral density and immune health benefits may be achieved by using a higher daily supplementation dose of 2000–4000 IU of vitamin D[10,11]. Many intervention studies have demonstrated the efficacy and safety of a daily dose of 2000–4000 IU of vitamin D3 supplementation during pregnancy in different populations, without any adverse side effects. A randomised controlled trial in the USA in which pregnant women (*n* 494) received either 400, 2000 and 4000 IU of daily vitamin D3 supplements from 12 to 16 weeks until delivery showed that, a daily dose of 4000 IU was the most effective in achieving vitamin D sufficiency (80 nmol/l or 32 ng/ml) throughout pregnancy and at the time of delivery, compared to the standard 400 IU, regardless of race and ethnicity[20]. Similar findings were reported in several intervention studies using a daily dose of 2000–4000 IU of vitamin D, including the USA in four different trials with multi-ethnic women[35–38], and other populations including women from Arab[32], New Zealand[31], Mongolia[33] and Iran[34]. A similar dose has also been safely used among non-pregnant adults[30].

Sources of vitamin D and their feasibility for pregnant women

Vitamin D can be obtained through dietary and endogenous sources. In the diet, it can be obtained from ergocalciferol (vitamin D_2) that originates from plant sources and cholecalciferol (vitamin D_3) that originates from animal sources. Fortified foods and supplements also provide vitamin D2 and D3. Sunlight is the main pathway of endogenous vitamin D production[9–11,13].

Sun exposure

Some experts recommend the ideal time frame for sun exposure to obtain vitamin D is between 11·00 and 13·00 h[48], while some argue that there is no agreement on what constitutes a safe and effective timeframe for sunlight exposure[10,15,13]. A midday direct sunlight exposure of 45 min to bare face, arms and legs without any sunscreen may enable the production of about 500

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IU of vitamin D. However, the endogenous vitamin D production from sunlight is variable with age, skin colour, sunscreen use, latitude, time of day and season[11,48,49]. Sunlight exposure as a source of vitamin D may not be feasible for pregnant women due to indoor lifestyles, use of sunscreen creams and Indian cultural practices of sun avoidance due to the fear of skin tanning, pigmentation and perceived risk of excess fatigue and dehydration during pregnancy[11,13,15,20].

Diet

Natural dietary sources of vitamin D are oily fish such as salmon, tuna, sardine, herring mackerel, trout and egg yolk and mushrooms (especially Maitake varieties). However, even a vitamin D-rich diet abundant in fish, for example, the diet of Greenlanders or Scandinavians, provides <10 % of one's vitamin D requirements of 400–600 IU[10,11,13,15,48]. Interestingly, the Bengali community in Eastern India also eat more fish than the rest of the Indians, but their vitamin D status too was reported low, like the rest of India[50]. An Indian study showed that even among the upper SES, the maximum intake of dietary vitamin D is <100 IU daily[51]. Generally, vitamin D is stable up to 200°C, but higher cooking temperatures on gas flames reach above 1900° C and time-consuming cooking practices in India may reduce the vitamin D content[13,15]. For example, it takes an average of 40 min to cook Indian fish curry. There are also other indirect dietary factors including lower calcium and higher salt, phytates and phosphates in Indian diets that may lower vitamin D absorption and utilisation[11,15]. A diet low in calcium in combination with insufficient vitamin D status is usually associated with secondary hyperparathyroidism, which increases the induced destruction of vitamin D [25(OH) D] and its substrate [1,25$(OH)_2$D] by the 24-hydroxylase enzyme[15,52]. A systematic review evaluating the global dietary calcium intakes of adults reported that Southeast Asia, including India, had one of the lowest daily median dietary calcium intakes (<400 mg), compared to higher intakes in Northern Europe (>1000 mg)[52]. Low calcium intakes in South Asia were also associated with lower circulating 25(OH)D levels[53]. Higher phytates and phosphates in an Indian diet can also reduce vitamin D reserves and increase calcium requirement[54]. Higher salt intake[15] in an Indian diet, estimated to be 11 g/d[55] (twice the recommendations of 5 g/d)[56] may also increase urinary calcium excretion. For the afore-mentioned reasons, natural dietary sources may not be feasible sources of vitamin D for the Indian population[9,11,14,16].

Vitamin D fortified foods

Worldwide, many staple foods including milk, oils, margarine, wheat starch, bread and breakfast cereals have been used as vehicles for vitamin D fortification[57]. A 2007 legislation on mandatory milk fortification of toned and double toned milk was passed by the Government of India, but limited progress has been made since then, and as a result, fortified foods are still rare and less affordable[11,14,57]. Vitamin D food fortification may be a viable strategy to address VDD[13,57]; however, even if more than one food item including milk, starch and ghee is fortified, the current permissible fortification dose of 20 IU/100 g is limited, and hence a majority may not meet their vitamin D requirements. Cooking oil may not be a suitable vehicle for fortification due to the degradation of vitamin D at very high cooking temperatures[15,16]. Evidence from the fortification programmes implemented in Canada and USA since early in the century have improved the vitamin D status of the populations, yet, VDD is still prevalent in a significant percentage of these populations[15]. Indian intervention studies exploring food fortification are sparse. Two fortification studies in healthy children have been reported[58,59], where laddoos (lentil-based fried Indian sweets) were fortified with 30 000 IU of vitamin D given monthly,[58] and milk fortified with 1000 IU of vitamin D given daily,[59] were effective in improving the children's vitamin D status.

Some data suggest that 25(OH)D levels in India vary from 25 to 46 nmol/l, and every 100 IU vitamin D3 will increase the serum 25(OH)D levels by 2·5 nmol/l, meaning an individual will need to consume 500–700 ml milk daily[57]. Although, the cost of food fortification is inexpensive (<5 Indian paise/GBP 0·009 for 1000 IU vitamin D3 per litre of milk)[57], the greater challenge is the affordable issue of foods such as milk or ghee to the socioeconomically underprivileged[15]. In the future, we need robust Indian evidence on food fortification from large interventions that are effective enough to be scalable at the public-health level, cost-effective for lower-income groups, and also feasible for pregnant women.

Antenatal calcium and vitamin D supplements

Antenatal calcium and vitamin D supplements containing 200–400 IU of vitamin D2 or D3 per tablet are routinely prescribed to all pregnant women from the end of first or the beginning of second trimester[42–45]. The 200–400 IU dose of vitamin D was probably aimed to enable calcium absorption[9,10,11,44], from the knowledge we had about vitamin D before a decade. But since then, vitamin D's role in human health has grown substantially beyond bone health[10,11,13,15].

Growing evidence calls for higher circulating levels of 25(OH)D and higher doses of vitamin D3 supplements (2000–4000 IU/d), not only for calcium absorption and bone health but many immunomodulatory benefits, including prevention of GDM and other positive maternal and child health outcomes[9,10,11,30–38,46,47,60].

The rationale for more attention for vitamin D in antenatal clinics in India

VDD is a global problem in sunshine-deficient and -sufficient regions[10–12,14]. Global scientific consensus acknowledges that: (i) the circulating 25(OH)D levels are widely accepted as the best marker of vitamin D status. (ii) The circulating 25(OH)D levels >50 nmol/l for all ages is marked as sufficiency[62]. (iii) Vitamin D

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supplementation during pregnancy improves the maternal vitamin D status which positively affects the 25 (OH)D availability to the fetus that easily crosses the placenta[10,11,61,62]. (iv) VDD may be associated with a higher risk of hyperglycaemia in pregnancy, GDM and other adverse pregnancy outcomes including gestational hypertension, preterm birth and poorer offspring health. (v) There is a need for maternal vitamin D screening and supplementation in antenatal clinics, but knowledge gaps exist about optimal blood levels (50–100 nmol/l), and the required vitamin D (400–4000 IU).

More intervention studies in the Indian population are needed to confirm the safety and efficacy of a daily dose of 2000–4000 IU vitamin D3 during pregnancy. However, in the absence of intervention studies in India, the available global evidence of higher vitamin D doses of 2000–4000 IU[9–11,30–38,46,47,60] may be extrapolated to the Indian population, who have very low circulating vitamin D levels, high prevalence of GDM, non-communicable diseases and chronic low-grade inflammation[3,11,15]. The evidence supporting higher circulating 25(OH)D levels and vitamin D requirements also indicate that vitamin D3 supplementation doses up to 10 000 IU daily have been safely used with minimal toxicity in adults[11,30]. Vitamin D toxicity with hypercalcaemia and hypercalciuria only occurred with elevated circulating 25(OH)D levels of >200 nmol/l and supplements administering >20 000 IU vitamin D daily[30].

It is clear that diet can provide <10 % of the vitamin D requirements, food fortification can deliver limited amounts, and hence optimal antenatal supplementation is the key. Prenatal calcium supplements containing 400 IU of vitamin D may be sufficient for calcium absorption and bone health, but may not provide immunomodulatory benefits, including GDM prevention. Higher vitamin D3 supplementation doses ranging between 2000 and 4000 IU may be delivered more easily by supplements than natural diet and the current limitations of fortification[10,11,46–48]. Also, only 10 % of the available antenatal calcium vitamin D supplements in the Indian market contain the vitamin D3 or cholecalciferol[63] that is more bioavailable[9–11] and considered an ideal prophylaxis formula in comparison to vitamin D2 in the treatment of VDD in all age groups globally[63].

Currently, VDD awareness and screening practices are low in antenatal clinics in India due to limited resources[11,13,15]. Present-day population-based screening may not be feasible or affordable for a large percentage of the people as the screening costs are currently high (INR 1000–4000/GBP 10–40)[13,15]. More research into low-cost vitamin D assessment techniques will reduce the cost of screening[10,11,13,15]. Vitamin D3 supplements of good quality should be made available at primary health care centres[11,14,15,63]. Investment in education, awareness, screening and supplementation of vitamin D for maternal and child health benefits is required[10,11,13,15,16,46,47,51,57].

Globally, policymakers have not paid enough attention to GDM, but in order to tackle the economic burden of non-communicable diseases, a top priority should be to make efforts towards improving the nutritional health of mothers, which will also be the stepping stone towards achieving the sustainable development goals[64,65]. The economic burden of non-communicable diseases in India is estimated to be about 10 % of India's gross domestic product[66] which amounts to INR 13·5 lakh crore or GBP 130·8 billion. Experts predict that vitamin D sufficiency of the Indian population alone can reduce the economic burden of non-communicable diseases including diabetes, CVD, cancer and osteoporosis-related bone fractures by 20–25%[57], that approximately amounts to INR 7 lakh crores or GBP 67·8 billion. This estimated amount is about thrice of the current Indian healthcare budget[66] and a large potential saving that can be directed to other developmental goals to improve food subsidy programmes, education and agriculture in India. We need to make a strong case for more attention for maternal VDD in antenatal clinics by investing efforts in education, research, screening and supplementation to build stronger evidence of benefit for vitamin D supplementation policies to prevent GDM.

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