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SHORT REVIEW

Potential impact of maternal vitamin D status on obstetric well-being

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Abstract Despite its discovery 100 years ago, vitamin D (VD) has emerged as one of the most controversial nutrients and prohormones of the 21st century. In the past few years, a growing interest in VD has been observed in the biomedical literature due to evidences demonstrating a relevant relationship not only between regulation of calcium and phosphorus homeostasis, but also multiple disease states and low VD status in the population. Indeed, several studies carried out to decipher its role in the body in almost every cell, tissue, and different organs. Recent findings suggested a significant implication of VD in different physiologic processes, such as vascular health, immune function, metabolism, and placental function. In the attempt to focus the attention on effect of VD on female reproductive health, there has been a paucity of data from randomized controlled trials to establish clear beneficial. Human and animal data suggest that low VD status is associated with impaired fertility, endometriosis, and polycystic ovary syndrome. Findings from observational studies show higher rates of preeclampsia, gestational diabetes, preterm birth, and bacterial vaginosis in women with low VD levels. By recent evidences, this review explored the association between maternal VD status and selected effects on maternal, perinatal, and infant health, and the impact of VD supplementation during pregnancy on obstetric well-being.

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Introduction

Vitamin D (VD) deficiency in the form of rickets was first described in the 17th century [1]. The "vitamin"—actually a fat-soluble steroid hormone—was not discovered until the early 20th century. In spite of its discovery, VD has emerged as one of the most controversial nutrients and prohormones of the 21st century. Indeed, if its role in calcium metabolism and bone health is undisputed, its influence on immune function and long-term health is debated [2–5] (Fig. 1).

The naturally occurring form of VD in humans is cholecalciferol or Vitamin D3 [6, 7] (Fig. 2). It can be ingested in the diet or produced in the skin by UV light interaction with a cholesterol derivative [8]. In contrast, Vitamin D2 or ergocalciferol is derived from plant sterols and is the form contained in most VD supplements [3]. Because these two forms have identical metabolism and function, in several studies, the term "vitamin D" is used to represent both vitamins D2 and D3 unless specified.

Both D2 and D3 circulate in the blood bound to a specific globulin, VD–binding protein, before the activation by hydroxylation. D2 and D3 metabolites are thought to have equal physiologic activity, but D3 levels may increase more quickly after supplementation [6–8]. Once ingested or produced by the body, D3 is transported to the liver for hydroxylation to 25-hydroxyvitamin D [25(OH)D], the main circulating form of VD and the best measure of VD status. The second hydroxylation to the active form 1,25-hydroxyvitamin D [1,25(OH)D] occurs mostly in the kidneys in a process tightly regulated by calcium, phosphorus, and

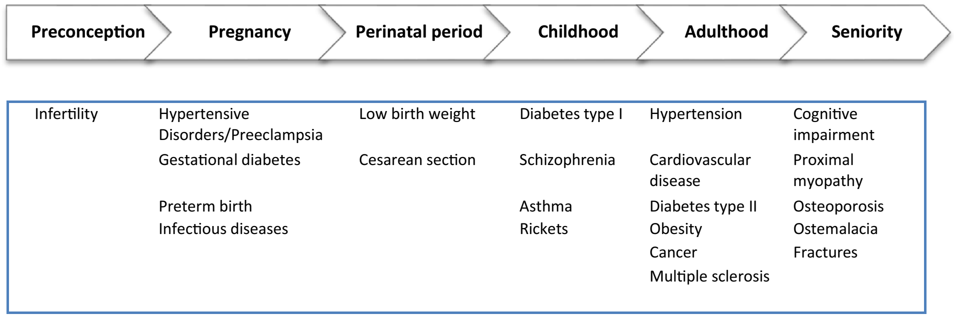

Fig. 1 Health implications of vitamin D deficiency at different stages

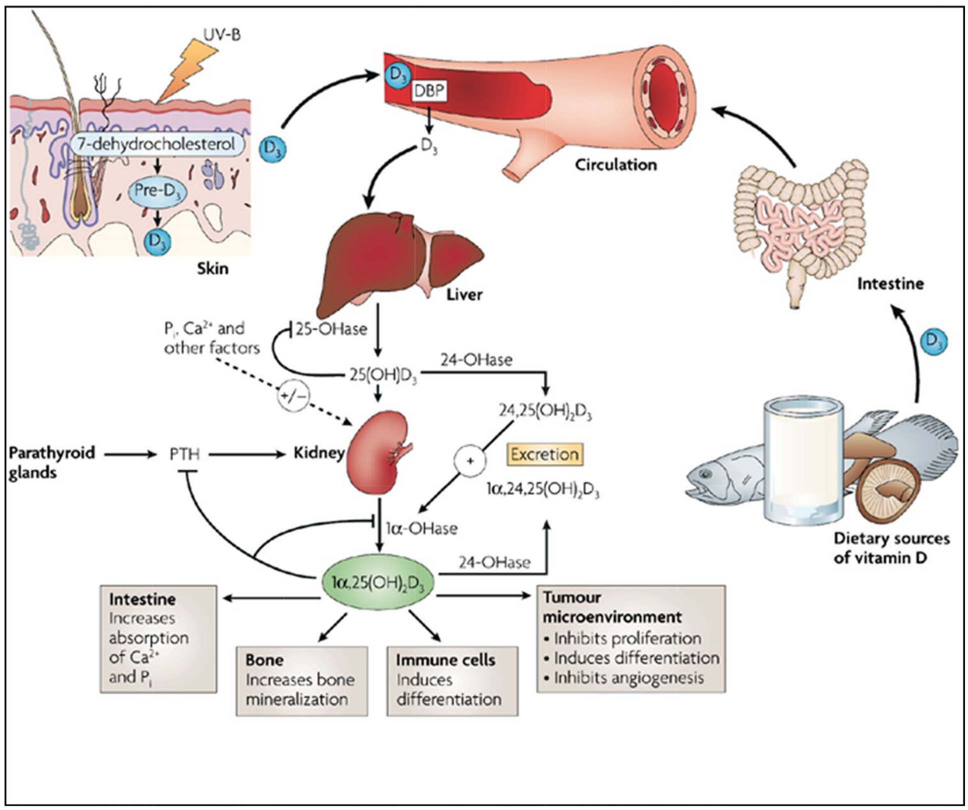

Fig. 2 Vitamin D metabolism. (By Deeb et al. Vitamin D signaling pathways in cancer: potential for anticancer therapeutics. Nature Reviews Cancer. 2007;7:684–700)

parathyroid hormone levels [9]. After the second hydroxylation, VD binds to the VD receptor (VDR). VDR is a transcription factor whose products are involved in a wide array of activities including bone metabolism, cellular growth and differentiation, glucose metabolism, and immune function [10]. Both the enzyme responsible for VD activation (1αhydroxyase) and its receptor have been located in peripheral tissues, such as the placenta, suggesting a farther reaching role for VD than bone metabolism alone [10].

Vitamin D physiology in pregnancy

During pregnancy, maternal serum levels of 1,25(OH)D increase up to twofold starting at 10–12 weeks of gestation and reaching a maximum in the third trimester [7]. Contrarily, it is unclear whether 25(OH)D levels increase during pregnancy [11]. However, given an increase in the active form of VD, pregnant women likely have a higher cellular exposure to VD during the second and third trimesters, suggesting a role for VD in obstetric well-being [7]. From a fetal point of view, the human fetus accretes 30 g each day on average, of which 99 % is contained within the skeleton [12]. More than 150 mg/kg of this calcium is actively transferred each day across the placenta during the third trimester [13]. For this double purpose, specific pregnancy-induced adaptations to maternal calcium homeostasis are implicated. Doubling the rate or efficiency of intestinal calcium absorption starting early in pregnancy appears to meet the fetal need for calcium [10]. Skeletal resorption can also provide mineral to the circulation, but evidence is mixed on whether the maternal skeleton contributes substantial amounts of calcium to the fetus [10, 11]. Bone resorption markers are modestly increased during pregnancy, and bone biopsies from women at the time of first-trimester abortions show histomorphometric evidence of increased bone resorption [11]. At renal level, it is not described any reclaim calcium during pregnancy; instead, urinary calcium excretion increases in parallel with the increase in intestinal calcium absorption [10].

Identifying vitamin D deficiency

Measuring VD insufficiency in pregnant women is complicated by a lack of agreement in some aspects, such as the accuracy of 25(OH)D levels as marker of deficiency, normal VD levels in pregnancy, and the identification of gold standard test for VD deficiency [14]. 25(OH)D is the clinical and research gold standard measure of VD status [15]. However, given the complexity of the VD system, it is unclear whether 25(OH)D levels have the same clinical implications in all women or throughout all stages of pregnancy [16]. Another suggestion by some researchers was to measure parathyroid hormone (PTH) levels as a biologic marker of VD deficiency, but PTH levels have been inconsistently associated with 25(OH)D levels pregnant women. [17] Recently, the Institute of Medicine defined adequate vitamin D status as having serum 25-hydroxyvitamin D concentrations greater than 50 nmol/l (or 20 ng/ml) in both the general population and pregnant women [18]. Some investigators propose that concentrations around 80 nmol/l (32 ng/ml) are optimal, since they suppress PTH levels and lead to the greatest calcium absorption and the highest bone mass, reducing the rates of bone loss, falls, and fractures [17]. However, it is uncertain whether these higher levels proposed for non-pregnant adults are also adequate for pregnant women.

Vitamin D deficiency and risk factors in pregnancy

There are a number of plausible biological pathways through which VD could influence maternal and fetal health during pregnancy. VD has important immune-modulating properties, helping to establish a proper maternal immune response to the placenta, reducing obstetrics risks associated to VD deficiency [19, 20].

Gestational hypertension/preeclampsia

Hypertensive disorders of pregnancy, especially preeclampsia (PE), are the most studied reproductive health outcomes in association with maternal VD status [2, 11, 21–24]. As known, PE is defined as the occurrence of hypertension and proteinuria after 20 weeks of gestation [25]. It occurs with a prevalence of 3–5 % of all pregnancies worldwide, representing the leading cause of maternal and fetal morbidity and mortality [25]. Taking into account the higher incidence in winter and a lower incidence in summer, seasonal patterns in PE suggest a role for VD and sunlight [24]. Compared with normal pregnancies, PE is characterized by marked changes in VD and calcium metabolism [21], and already in the early 1990's, a role for VD in the pathogenesis of PE was hypothesized [26]. Women with PE are known to have lower circulating 25(OH)D3 levels than normotensive pregnant women [21–23]. In nested case–control studies, VD deficiency in pregnancy <50 nmol/l of 25(OH)D3 was associated with an almost fourfold odds of severe PE [22], and VD deficiency <37.5 nmol/l was even associated with a fivefold risk of developing PE [27]. Bodnar et al. showed that 25(OH)D3 deficiency before 22 weeks of gestation is an independent risk factor for the manifestation of PE [27]. In addition, Robinson and coll. reported lower maternal 25(OH)D3 concentrations in 56 women with early onset PE and small for gestational age (SGA) infants vs. infants with normal fetal growth, suggesting an impact of VD on fetal growth through placental mechanisms [23].

VD supplementation studies to prevent PE showed protective effects of VD [28–32]. The first known study in this context was a controlled trial in London in the 1940–1950's with 5644 women in which a reduction of 31.5 % in PE was seen in women who received a dietary supplement containing vitamins (2500 IU of VD), minerals, and fish oil in comparison to the control group who did not receive any supplement [28]. In a cohort of 23,423 nulliparous women in Norway, Haugen et al. showed a 27 % reduction in the risk of PE in women who took 400–600 IU VD supplements per day compared to women without supplementation [29].

In reproductive health, in a Finish birth cohort, it was observed that VD supplementation early in the first year of life is associated with a 50 % reduction of PE prevalence in the first pregnancy later in life [30]. This suggests that VD intake in infancy may be involved in programming processes of the immune system. One mechanism suggested is the regulation of maternal and placental immunological and inflammatory responses, as it has been shown in experimental models [31, 32]. In syncytiotrophoblasts from preeclamptic pregnancies, the expression and activity of 1a-hydroxylase are restricted suggesting an important role for VD at the placental site of the disease [33], and endorsing the VD role in the regulation of target genes associated with implantation, trophoblast invasion, and implantation tolerance [34]. Regarding implantation tolerance, Th2 cell induction is one of the critical steps required for the maintenance of normal pregnancy, whereas impaired implantation and adverse reaction of maternal metabolism to the fetus in PE are mediated by Th1-cytokines [35]. This fetal placental interface may be influenced by VD, which has an important role in promoting the shift to a Th2-dominated immune response pattern [35]. The maternal response to reduced placental perfusion in PE may equally be affected by VD. Maternal VD deficiency may lead to the increased inflammatory response that characterizes PE as well as to endothelial dysfunction through direct effects on angiogenesis gene transcription, including vascular endothelial growth factor (VEGF) [36].

Gestational diabetes

Gestational diabetes mellitus (GDM), a common pregnancy complication defined as glucose intolerance with onset or first recognition during pregnancy, affects approximately 7 % (ranging from 1 to 14 %) of all pregnancies [37]. GDM is related to increased risk of adverse obstetric outcomes and has substantial long-term adverse health impacts on both women and their offspring, including an elevated risk for Type 2 diabetes mellitus in later life among women and an increased risk for childhood obesity and impaired glucose tolerance among offspring [37].

Polymorphisms of VD have been associated with metabolic mechanisms: a genetic contribution of CYP27B1 polymorphisms may modulate 25(OH)D3 levels in GDM patients [38]. In a nested case–control study 25(OH) D3 levels <50 nmol/l at 16 weeks gestation before the onset of GDM was associated with a 2.7-fold increased risk for the development of GDM later in pregnancy [39]. At the time of oral glucose tolerance testing at mid gestation, two reports noted significantly positive correlations between 25(OH)D3 concentrations and insulin sensitivity or fasting/2-hour blood glucose levels and HbA (1c) [40, 41]. Interestingly, after 1,25(OH)2D3 supplementation alone [42], similarly to physical exercise [43], a decrease in glucose and insulin levels was noted; therefore, RCTs of VD supplementation, initiated early in pregnancy, are required to demonstrate the therapeutic role of VD supplementation in terms of reduced incidence of GDM.

Preterm delivery

VD has immunomodulatory and anti-inflammatory effects, such as the regulation of production and function of cytokines and neutrophil degranulation products, both relevant to prevent microbial invasion associated to protective role on preterm delivery (PD) [44, 45].

From a pathophysiological point of view, there are numerous reasons for PD, including intrauterine infection and inflammation [46, 47]. One major factor is the presence of bacterial vaginosis, a disruption of the normal balance of vaginal flora with increased growth of anaerobic bacteria responsible for the release of inflammatory cytokines, prostaglandins, and phospholipase A2 [46]. A recent study including 3523 women showed the relationship between 25 (OH)D3 deficiency (<75 nmol/l) and bacterial vaginosis among pregnant women [48].

VD has key actions that enhance the innate immune system, even if its action dampens the activation of the acquired immune system in response to autoimmunity. It is involved in cell-mediated immunity by reducing the production of inflammatory cytokines, such as IL-1, 6 and TNF, related to PB [44, 49, 50]. Additionally, VD might reduce the risk of PD also by helping to maintain myometrial quiescence [50]. Indeed, myometrial contractility is dependent on calcium release within the muscle cell and this process is regulated by VD. Although experimental data are promising, there are limited observational data available on the linkage VD-PD [51]. In a first-trimester cohort of 4225 women with 40 cases of PD ≤ 34 weeks, the prevalence of VD deficiency (25 (OH)D3 < 50 nmol/l) was comparable among women who subsequently delivered preterm compared with controls [52]. In a cohort of 82,213 singleton live births indirect evidence that VD and seasonal sunlight exposure are relevant for PD were found. PD prevalence was the lowest among women who conceived in summer and fall and was the highest among winter and spring conceptions [27]. More large studies are awaited to validate these important findings that might represent VD supplementation as a simple and inexpensive method to reduce the risk of this adverse pregnancy outcome.

Mode of delivery

Severe VD deficiency and rickets cause pelvic deformities, which have been known for many years to increase the risk of obstructed labor. There are contrasting results in the literature regarding this aspect [9–11]. In 2009, a study of 300 women found that severely VD-deficient women with levels of 25(OH)D3 < 37.5 nmol/l delivered nearly four times as often by cesarean section (CS) than those with 37.5 nmol/l or greater (OR 3.84), while a RCT of VD supplementation found no difference in CS rates between treatment and control groups [53]. No association was found between obstructed labor ensuing CS and VD status in a case–control study of nulliparous women at term [54]. These are the only studies so far examining VD status in pregnancy and mode of delivery, and therefore, the issue needs further investigation.

Fetal programming

VD induces more than 3000 genes, many of which play a pivotal role in the "fetal programming hypothesis", in which environmental factors can influence the genomic programming of fetal and neonatal developmental and subsequent disease risk in both childhood and adulthood [55]. Interestingly, in later life, children of mothers with low VD serum levels during pregnancy suffer more often from chronic diseases, such as wheezing and asthma, schizophrenia, multiple sclerosis, type 1 diabetes mellitus, and insulin resistance. Mechanisms underlying this long-term effect of the intrauterine environment are not known yet, but epigenetic mechanisms that lead to persistent changes in structure and function in endocrine systems are hypothesized [56].

Study results have been mixed both for the association between low birth weight (BW) and VD status at delivery and between low BW and first-trimester 25(OH)D levels. The largest cohort study of 3730 women found the odds of birthing a baby small for gestational age (SGA) was higher among women with severe VD deficiency in early pregnancy (<12 ng/l) [57]. However, no studies fully controlled for sun exposure or dietary factors. Taken together, these data suggest that if an association between VD status and infant BW exists, it may vary according to subgroups, such as severe VD deficiency or race. Pooled analyses indicated significantly greater average daily weight gain in the third trimester among women supplemented with VD, and a non-statistically significant 33 % decrease in the risk of SGA [28, 58]. However, an observational cohort study reported no difference in BW for gestational age by quartile of VD intake in unadjusted analysis [55]. Prospective observational studies of VD status and SGA have had mixed findings [59, 60]. However, the largest study to date found that the risk of SGA among VD-deficient women (25(OH)D <30 nmol/l) was nearly twice that of women with adequate status in multivariate adjusted models (AOR 1.9 [95 % CI: 1.4, 2.7) [61].

In postnatal life, one supplementation trial in the UK reported significantly greater weight gain among infants born to women supplemented with VD compared with the placebo group 3, 6, 9, and 12 months [62]. Up to 6 months of age, there were no differences in attained height between groups, but by 1 year of age, those in the VD group had grown 27.9 vs. 24.6 cm in the placebo group ($p < 0.001$) [62]. A large observational study in the Netherlands found no differences in multivariate adjusted mean weight-for-age z-scores by category of maternal VD status during pregnancy at any measure taken during the first year of life [70]. While infants born to mothers with 25(OH)D levels <30 nmol/l had significantly lower mean length for age z-scores at 1 month compared with those born to women adequate status (>50 nmol/l), paradoxically they had higher z-scores by 12 months with no differences observed at 3, 6, or 9 months [63]. A cohort study of the effects of maternal VD status during pregnancy on subsequent outcomes found no differences in attained weight or length at 9 months of follow up across quartiles of 25(OH)D status measured in late pregnancy [64]. However, in a linear regression model examining predictors of height at 9 months that included height measured at birth, a significant association with maternal 25(OH)D was observed ($p = 0.02$) [64].

Regarding neonatal and infant morbidity, VD supplementation during pregnancy seems to improve pediatric health. A study of 922 infants found significantly greater risk of respiratory infection (a composite variable of colds, cough, whooping cough, chest infections, and ear infections) by 3 months of age among infants with cord blood levels of 25(OH)D less than 25 nmol/l in adjusted analysis compared with levels at or above 75 nmol/l, OR = 2.04 [1.13, 3.17] [65]. In contrast, a cohort study followed up children at age 9 months found that mothers in the top quartile of 25(OH)D status in late pregnancy were significantly more likely to report their children having been diagnosed with pneumonia or bronchiolitis, compared with those in the bottom quartile [unadjusted OR 4.80, (1.01, 22.73)], although no differences in risk for respiratory infections overall or for chest infections or bronchitis were observed [64]. The same study unexpectedly also found that children of mothers in the highest quartile of VD status were more likely to have reported having one or more bouts of diarrhea vs. those in the bottom quartile [OR = 1.87 (1.01, 3.46)] [64].

Treating vitamin D deficiency in pregnancy

VD supplementation, fortified foods or specific supplements are crucial, especially in the winter at northern latitudes. Since VD can also be synthesized by the skin upon exposure to sunlight, increasing casual sun exposure for reaching the optimal serum levels has been recommended (Table 1). However, as excessive UV radiation is a carcinogen, it might be worth obtaining additional VD from foods or supplements. Dietary recommendations are available in many European countries, US and globally.

Pregnant women, neonates, and infants form the most vulnerable groups for VD deficiency. As previously described, VD deficiency may put pregnant women at greater risk for PE, PD GMD and infections, and poor weight gain. For that reason, the clinical significance of vitamin D supplementation as a part of routine antenatal care must be considered. Supplementation studies conducted with recommended daily allowance of 400 IU have not shown any improvement in vitamin D status of pregnant women [14]. Higher doses given as a daily dose of 800 IU or bolus dose of 200,000 IU given as a single dose or 2/3 divided doses given once a month have shown significant improvement [14]. However, even in these studies, adequate

Table 1 Recommended Dietary Allowances (RDAs) for vitamin D

Age	Male	Female	Pregnancy	Lactation
0–12 months	400 IU (10 mcg)	400 IU (10 mcg)		
1–13 years	600 IU (15 mcg)	600 IU (15 mcg)		
14–18 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
19–50 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
51–70 years	600 IU (15 mcg)	600 IU (15 mcg)		
>70 years	800 IU (20 mcg)	800 IU (20 mcg)		

(Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. 2011) [18]

levels were achieved in only 30 % of the participants [66, 67]. In another randomized controlled trial, women with a singleton pregnancy at 12–16 weeks' gestation received 400, 2000, or 4000 IU vitamin D3/day until delivery, with 68 % females achieved 25(OH)-D level ≥80 nmol/l at delivery with 4000 IU vitamin D3/day compared to 43 % females who achieved 25 (OH)-D level ≥80 nmol/l at delivery with 400 IU vitamin D3/day of supplementation [68].

Evidences from a single-centers, open-label, randomized, controlled trials of routine care in high-risk obstetric population, such as in Pakistan [68], Brazil [69], or India [71], treated with VD supplementation daily, reported an improved maternal and neonatal VD status and reduction of adverse perinatal outcome. In Europe, a randomized controlled trial, for preventive measures against the development of GDM in overweight and obese women, is exploring the potential effectiveness of VD supplementation on the risk of developing GDM combined by lifestyle [72]. In contrast, in Australia, a double-blind, randomized controlled trial of low vs. high dose of VD supplementation, concluded that high dose does not improve glucose levels in pregnancy [73].

In order to improve obstetrical outcomes, some health organizations recommend VD supplementation during pregnancy and lactation [15, 19]. However, there is controversy regarding the 25-hydroxyvitamin D levels that are considered adequate or optimal for overall health. In its 2011 report, the IOM recommended 600 IU per day of 25(OH)D for pregnant women specifically to support bone metabolism and no more than 4000 IU per day to avoid hypercalcemia [19]. ACOG endorses these recommendations and proposes 1000–2000 IU per day of 25(OH)D when deficiency is identified (<20 ng/ml) [15].

Conclusion

VD deficiency is still considered a problem for different parts of the populations, including infants, children, pregnant, and postmenopausal women. Besides the classical diseases, such as rickets, osteoporosis, and osteomalacia, VD deficiency in women might be associated with lower fertility and increased risk for adverse obstetric outcomes. Available scientific data are limited and well-conducted clinical trials without discrepancies in terms of genetic, ethnic, and racial differences, latitude of residence and season, standardization of potential confounding factors, and adequate length of follow up are still lacking. In women's reproductive health, a potential effect of VD supplementation has been described, but we need high quality evidence relating to clinical effects during pregnancy, before a routine supplementation. For this purpose, further rigorous randomized trials are required to evaluate the association between increased level of serum 25-hydroxyvitamin D and obstetric outcomes.

Conflict of interest S. Triunfo and A. Lanzone declare no conflict of interest.

Ethical approval (research involving human participants and/or animals) Not required due to type of manuscript (review).

Informed consent Not required due to type of manuscript (review).

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