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EDITOR'S NOTE

Editor's Note concerning Letter to the Editor by DE Roth and Response to Letter to the Editor by V Bhatia *et al.*

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Following the publication of a paper titled 'Vitamin D replacement in pregnant women in rural North India: a pilot study' by Sahu *et al*. (*Eur J Clin Nutr* 63, 1157–1159), a Letter to the Editor was received from DE Roth (doi:10.1038/ejcn.2010.1). The Letter and a Response to the letter by the authors, led by the corresponding author V Bhatia (doi:10.1038/ejcn.2010.2), were published online in February 2010 and follow this note in this print issue. A matter related to corrections that were made to the initial Letter to the Editor by Roth at the proof stage was raised by the respondent, which implied that the corrections made at this late stage to the letter altered the very essence of the debate that followed the original publication of the pilot study. We have hence decided to set the record straight by providing this note at the time of the print publication of this correspondence in our journal.

In the last paragraph of the original letter submitted to the journal, Roth states, 'it remains unknown whether maternal vitamin D deficiency affects fetal well-being or development in humans, regardless of observed changes in 25(OH)D concentration'. The final letter by Roth corrected at the proof stage and subsequently published online, however, reads, 'it remains unclear how maternal vitamin D supplementation affects fetal well-being or development in humans, regardless of observed changes in 25(OH)D concentration'. The fact that Bhatia and colleagues have quoted the sentence from the original letter from Roth in the last paragraph of their response demonstrates that they were responding to the statement in the original letter, and not that in the corrected proof.

In fairness, it is likely that the original letter by Roth was meant to refer to the issue of maternal vitamin D supplementation rather than to maternal vitamin D deficiency, for the consequences of the latter are well recognized, as pointed out by the respondents. However, making these important changes at the proof stage undermined the fair attempt at rebuttal by the respondents, which is the reasoning behind this note. We hope we have set the record straight.

We encourage letters and correspondence debating scientific issues arising out of publications in our journal. Although we also entertain correspondence raising other issues such as ethical considerations or conflicts of interest, we will not publish such correspondence, but will follow up, investigate and deal with them internally.

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LETTER TO THE EDITOR

Vitamin D replacement in pregnant women in rural north India: a pilot study

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The recent on-line publication in *EJCN*, 'Vitamin D replacement in pregnant women in rural north India: a pilot study' (Sahu *et al*., 2009), does regrettably little to advance our understanding of the safety and efficacy of antenatal vitamin D supplementation. The design of the study overlooked existing knowledge of vitamin D pharmacokinetics. Following a single oral dose of 50 000–100 000 IU vitamin D3, the

average 25-hydroxyvitamin D (25(OH)D) concentration rises to a peak within 2 weeks, then gradually declines towards the baseline concentration over a period of about 2 months (Armas *et al*., 2004; Ilahi *et al*., 2008). The single dose of 60 000 IU D3 administered by Sahu *et al*. in the 5th month of gestation would not be expected to have a perceptible effect on 25(OH)D concentrations in most women at delivery, which was the only time at which the biochemical response was assessed. Even the larger doses administered later in pregnancy would have been predicted to have minor effects on the 25(OH)D concentration measured at delivery, despite almost certainly having caused important but undetected elevations in 25(OH)D concentration during the third trimester. Therefore, it is incorrect to conclude from Sahu *et al*.'s report that the reported supplement regimens had little or no effect on vitamin D status during pregnancy.

The interpretation of the data is further complicated by the unspecified variation in the precise length of the interval between D3 dosing and 25(OH)D measurement among participants. The simple average 25(OH)D concentration at delivery reported by the authors is not a meaningful estimate of a time-dependent biochemical outcome.

Sahu *et al*. (2009) did not report measures of maternal or fetal safety, which have not yet been firmly established for high-dose vitamin D supplementation during pregnancy. As with measures of biochemical efficacy, the timing of safety assessments is crucial. The risk of maternal hypercalcemia was low for the doses selected, but would be highest when the circulating concentrations of vitamin D metabolites collectively exceed the capacity of the vitamin D binding protein (Kimball and Vieth, 2008), which would most likely occur within the first 2 weeks after dose administration. Sahu *et al*. (2009) only reported maternal serum calcium concentration at delivery, thus missing the relevant window of exposure. Moreover, as it is unknown whether fetal safety is exclusively related to maternal calcium homeostasis, it is incumbent upon antenatal vitamin D trial investigators to perform and report measures of fetal development (for example, birth anthropometry, neonatal examination for congenital anomalies), perinatal outcomes and, ideally, longer-term developmental follow-up.

The authors' notion that 'it was unethical to continue with a group not receiving any cholecalciferol' Sahu *et al*., 2009) is not well founded, particularly given the design flaws noted above and the lack of health outcome measures in their study. Clinical equipoise exists, as it remains unclear how maternal vitamin D supplementation affects fetal well-being or development in humans, regardless of the observed changes in 25(OH)D concentrations. Therefore, rigorous placebo-controlled trials of antenatal vitamin D supplementation are an ethical research strategy that should be implemented to establish the role of vitamin D status in maternal–fetal health in South Asia.

Conflict of interest

The author declares no conflict of interest.

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References

Armas LA, Hollis BW, Heaney RP (2004). Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab* **89**, 5387–5391.

Ilahi M, Armas LA, Heaney RP (2008). Pharmacokinetics of a single, large dose of cholecalciferol. *Am J Clin Nutr* **87**, 688–691.

Kimball S, Vieth R (2008). Self-prescribed high-dose vitamin D(3): effects on biochemical parameters in two men. *Ann Clin Biochem* **45**, 106–110.

Sahu M, Das V, Aggarwal A, Rawat V, Saxena P, Bhatia V (2009). Vitamin D replacement in pregnant women in rural north India: a pilot study. *Eur J Clin Nutr* **63**, 1157–1159.

RESPONSE TO LETTER TO THE EDITOR

Response to letter to the editor 2009EJCN0381 (Roth)

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We thank Roth (2010, this issue) for his comments. Ours was a pilot study, as indicated in the title. As we have already mentioned in the shortcomings of our study, larger randomized studies with different dosage schedules and testing time points are definitely needed to establish dosage and toxicity issues in pregnancy. Logistic considerations did not allow us to address some of these issues. Furthermore, as

mentioned in the paper, we wished to coincide the administration of the vitamin D doses with the routine antenatal visits of the community health worker in India, to allow the results to be extrapolated to clinical practice.

As regards the literature cited by Dr Roth, the report by Armas *et al*. (2004) was a study of serum 25-hydroxyvitamin D (25(OH)D) till only 1 month after vitamin D dosing, but not longer. The study by Ilahi *et al*. (2008) (and also by Romagnoli *et al*., 2008) is useful to illustrate the pharmacokinetics of 25(OH)D after administration of a single oral large dose of vitamin D3, and we agree with their suggestion that the levels of 25(OH)D are maintained above baseline for a little beyond 2 months after an oral dose. These results were published only when our study was almost complete. Notwithstanding these facts, in our study, women in group C did have significantly higher levels of 25(OH)D at delivery than at baseline, and in comparison with other groups.

We are surprised to read Dr Roth's words 'as it remains unknown whether maternal vitamin D deficiency affects fetal well-being or development in humans, regardless of the observed changes in 25(OH)D concentrations', in view of the published literature on fetal growth, neonatal hypocalcemia and bone density in childhood, among others (Brooke *et al*., 1980; Delvin *et al*., 1986; Marya *et al*., 1988; Javaid *et al*., 2006). As regards the ethics of withholding vitamin D during pregnancy, (a) the prevalence of vitamin D deficiency in adolescent girls and pregnant women in north India is overwhelming (Marwaha *et al*., 2005; Sachan *et al*., 2005; Sahu *et al*., 2009); (b) cord blood 25(OH)D mirrors this situation (Sachan *et al*., 2005); and (c) the consequences of *in utero* and infantile vitamin D deficiency are well established. All experts in the subject advocate replenishment during pregnancy for vulnerable populations. The question, in our mind, is not whether to supplement the vitamin, but by how much.

Conflict of interest

The authors declare no conflict of interest.

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References

Armas LA, Hollis BW, Heaney RP (2004). Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab* **89**, 5387–5391.

Brooke OG, Brown IR, Bone CDM, Carter ND, Cleeve NJ, Maxwell JD *et al.* (1980). Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *Br Med J* **280**, 751–754.

Delvin EE, Salle BL, Glorieux FH, Adeleine P, David LS (1986). Vitamin D supplementation during pregnancy: effect on neonatal calcium homeostasis. *J Pediatr* **109**, 328–334.

Ilahi M, Armas LA, Heaney RP (2008). Pharmacokinetics of a single, large dose of cholecalciferol. *Am J Clin Nutr* **87**, 688–691.

Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Boucher BJ *et al.*, Princess Anne Hospital Study Group (2006). Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet* **367**, 36–43.

Marwaha RK, Tandon N, Reddy DR, Aggarwal R, Singh R, Sawhney RC *et al.* (2005). Vitamin D and bone mineral density status of healthy schoolchildren in northern India. *Am J Clin Nutr* **82**, 477–482.

Marya RK, Rathee S, Dua V, Sangwan K (1988). Effect of vitamin D supplementation during pregnancy on foetal growth. *Indian J Med Res* **88**, 488–492.

Romagnoli E, Mascia ML, Capriani C, Fassino V, Mazzei F, D'Erasmo E *et al.* (2008). Short and long term variations in serum calciotropic hormones after a single very large dose of ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) in the elderly. *J Clin Endocrinol Metab* **93**, 3015–3020.

Roth DE (2010). Response to 'Vitamin D replacement in pregnant women in rural north India: a pilot study'. *Eur J Clin Nutr* **64**, 914–915 (this issue).

Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, Bhatia V (2005). High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. *Am J Clin Nutr* **81**, 1060–1064.

Sahu M, Bhatia V, Aggarwal A, Rawat V, Saxena P, Pandey A *et al.* (2009). Vitamin D deficiency in rural girls and pregnant women despite abundant sunshine in northern India. *Clin Endocrinol* **70**, 680–684.