Time to implement vitamin D assessment and supplementation into routine obstetric practice?

Vitamin D deficiency (25-hydroxyvitamin D concentration < 20 ng/mL) is the most common nutritional deficiency in the world, although vitamin D is one of the most well-understood compounds. Vitamin D is known to reduce the risks of many adverse health outcomes through both genetic and nongenetic mechanisms and it is readily available from supplements that are safe and inexpensive. However, the beneficial effects of vitamin D for patients with nonskeletal disorders have received widespread attention from researchers since 2000 (1).

Tamblyn et al. (2) conducted a systematic review and meta-analysis with the aim of investigating whether adequate vitamin D status protects from pregnancy loss. The study included 6 observational studies and 4 randomized controlled trials (RCTs). The rationale for this aim has strong biological plausibility because low vitamin D levels have been associated with several reproductive disorders, including endometriosis; polycystic ovary syndrome; uterine fibroids; and adverse obstetrics outcomes, such as preeclampsia, gestational diabetes mellitus, and preterm birth (2).

The study showed that vitamin D deficiency or insufficiency during pregnancy is associated with a higher miscarriage rate. The magnitude of risk progression in pregnancies with vitamin D deficiency or insufficiency ranged on average between 60% and 90% as compared to those with vitamin D repletion, showing a biological gradient with higher effect (risk of miscarriage) associated with greater depletion. Although the planned subgroup meta-analysis for preconception vitamin D assessment and the risk of recurrent miscarriage failed (because only 1 eligible study could be identified), the study established additional robust evidence for major effects of vitamin D in early human pregnancy and raised a call for future investigation in this area.

However, the study is not devoid of limitations, as correctly disclosed by the investigators (2). The inclusion of miscarriage cases with likely different etiologies, such as those occurring in the first trimester (mostly due to chromosomal defects) or second trimester (due to cervical insufficiency or other factors) as well as recurrent pregnancy losses (often due to combinations of parental chronic conditions), increased the heterogeneity of the outcomes. Therefore, the "dilution" of the real effect of vitamin D on the risk of miscarriage may be expected, with consequent minimization of statistical significance. Moreover, further sources of heterogeneity can be recognized based on diverse classification of vitamin D deficiency and at different timings of assessment, as the investigators correctly admitted. These limitations represent reasons for caution, but they do not diminish the biological and clinical importance of these findings. Instead, as mentioned above, they may support the hypothesis that the association between low vitamin D levels and miscarriage risk demonstrated by Tamblyn et al. (2) would be smaller than that expected after the exclusion of cases because of etiologies unrelated to the biological action of vitamin D (e.g., chromosomal defects). The occurrence of chromosomal defects as a consequence of vitamin D deficiency has not been proven and is biologically questionable. Therefore, cases with a genetic basis should be excluded from future studies assessing the risk of miscarriage based upon vitamin D levels or attempting its prevention by supplementation. Conversely, the recognized effects of vitamin D on the developing receptive endometrium, the immune system, thrombosis or hemostasis phenomenon, cardiovascular health, and placental function are all potentially critical to the risk of miscarriage (1). Finally, given the association between vitamin D deficiency or insufficiency and preterm birth, a potential mechanism involved in early cervical insufficiency underlying pregnancy loss cannot be excluded (3). This observation was enough to support pooling data derived from first and second trimester miscarriages, but we would like to recommend subgroup analyses as soon as information is available from future well-designed trials on this topic.

Notably, in studies evaluating the role of vitamin D in human health, some aspects need to be considered. Although observational studies can suggest that better provision of vitamin D is strongly associated with reductions in several health risks, RCTs frequently fail to provide supportive evidence for the expected health benefits of supplementation (4). In the field of reproduction, an example is represented by studies assessing the impact of vitamin D on the success rates of assisted reproductive technology procedures. Although observational, prospective, and retrospective studies were in strong support of a beneficial role of the vitamin, the RCT with the largest sample size and using high-dose supplementation was not able to confirm these findings (5). There are various reasons for these difficulties in conducting well-designed RCTs to demonstrate treatment effects. First, vitamin D is a nutrient and not a drug, and the corresponding physiologic response has a sigmoid curve. This means that at low intake, a little response is generated; the effect increases fairly rapidly for a particular amount of intake or exposure range, and then at higher intake, the response reaches a plateau. Therefore, in RCTs in which identical doses are administered to all subjects in the treatment arm, the doses will be too small to normalize the levels of the vitamin in many patients with deficiency and will be unable to induce a detectable response in those who with repletion (4). The possibility to measure relevant health benefits in the treatment arm is obviously reduced in patients with these conditions. Another potential problem related to RCTs refers to the vitamin D threshold effect. Although the currently used serum threshold for bone health is well established, nonskeletal health may benefit from higher levels. The threshold required to limit the risk of spontaneous abortion is completely unknown, and the failure to ensure and maintain the

adequate level for the outcome of interest during RCTs represents a confounder. Other potential reasons for the failure of RCTs include poor attention to conutrient status, which is often important in studies of nutrient efficacy; the role of genetic polymorphisms contributing to the modulation of the action of vitamin D in target tissues; and the adjustment of the doses and timings to ensure a planned status in relation to population characteristics (4).

Tamblyn et al. (2) were not able to pool data from selected RCTs focused on vitamin D treatment. The 4 studies were characterized by great disparity among the regimens used by reporting the bias and other problems preventing a direct comparative analysis. A preconception intervention was foreseen only in 2 of the studies. Notably, in line with the aforementioned observations, none of the studies was able to observe a significant effect of vitamin D supplementation on the reduction of the miscarriage rate. An RCT by Samimi et al. (included in the meta-analysis object of this commentary) indeed found a significant reduction in the miscarriage rate after vitamin D supplementation in a population of women with unexplained recurrent spontaneous abortion. However, after correcting for confounding factors in the logistic regression analysis, the effect of vitamin D on the incidence of abortion was no more statistically significant.

Is it time to implement vitamin D assessment and supplementation into routine obstetric practice? We believe that there is probably enough evidence for promoting the measurement of vitamin D levels before conception or in the first trimester of pregnancy (if this was not done earlier) as a prognostic biomarker for miscarriage. On the other hand, it is not yet proven that correcting the vitamin D levels may reduce miscarriage risk. The difficulties in ensuring that RCTs with appropriate designs are conducted do not, however, justify the acceptance of deficiency.

Well-designed RCTs on intervention with vitamin D should identify outcomes a priori excluding those linked to unrelated etiologies, assess preconception nutritional status and vitamin D levels, define appropriate dosages minimizing threshold effects, and check very carefully the issue of power because the nutrient effect tends to be small. It is intuitive that the results of null-effect studies affected by flaws may reduce confidence with regard to the nonskeletal health benefits of vitamin D, for which deficiency is avoidable through simple measures.

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