Accumulating evidence for vitamin D and conception

In this issue of *Fertility and Sterility* researchers from Denmark present an ecologic analysis of a mandatory vitamin D fortification program that began in 1962 and abruptly ended in 1985 (1). Among women with an infertility diagnosis, they report increased odds of live birth during the last years of the fortification period (1980–1985) compared with a subsequent non-exposed time period (1986–1991). The finding was robust to several sensitivity analyses. The ecologic design is limited, as any other trends over time could confound the results. For example, rates of sexually transmitted infections tended to decrease from the fortification period to the post-fortification period. This trend would increase the probability of live birth during the post-fortification period resulting in confounding towards the null. Changes over time in the diagnosis and treatment of infertility, and the accessibility of infertility care, could also influence the results. If women started seeking infertility treatments sooner in their pregnancy attempts during the later time period compared with the fortification period, the observed association would be biased toward the null. However, if the diagnosis of infertility became stricter over time, for example, if over time women were told to wait until their pregnancy attempt was unsuccessful for at least 12 months, then this could produce the observed association. Additionally, body mass index may have, on average, increased in the population from the early to late 1980s which would be expected to produce a positive, spurious, association with fortification, although these changes are likely to be small.

Figure 1 suggests that the chance of live birth among women diagnosed with infertility started to decline in 1984, before the end of the fortification program in mid-1985 (1). This argues that other factors may have initiated the observed trend before the exposure period ended. An additional point for interpreting the results of this study is that vitamin E fortification was discontinued at the same time as vitamin D fortification, and thus it is not possible to separate their effects. Interestingly, this study did not examine male partner infertility during and after fortification. It is possible that male reproductive function is influenced by vitamin D. Vitamin D has been reported to increase sperm motility and semen quality (2).

Although ecological studies are difficult to interpret causally, natural experiments like the one reported here, offer unique opportunities to explore and generate hypotheses. Other countries with a comparable ability to link health care databases that also implemented changes in food fortification policy would provide a useful replication. Finland may offer an opportunity given their commencement of vitamin D fortification starting in 2000 (3). Future studies could consider defining the outcome based on the timing of conception, rather than the timing of birth, to avoid a selection bias towards shorter gestations. Future work would also be enhanced through inclusion of data on other sources of vitamin D, and their trends over time, in the specific population under study. These might include the use of tanning beds, vitamin supplements, or cod-liver oil and other regionally specific vitamin D rich foods.

There is a growing literature linking vitamin D and female reproduction. Animal studies have reported reduced ovulation and fertility in vitamin D deficient models (3, 4). At the same time, community-based human studies have linked higher 25-hydroxyvitamin D (25OHD) and lower risk of menstrual cycle abnormalities and a higher probability of conception (3, 4). These studies, however, are just the beginning. Unanswered questions remain regarding the underlying biological pathways and the dose-response association between 25OHD and conception.

The biological pathways by which vitamin D influences reproductive function are largely unknown. Few in vivo human studies have been done to identify physiologic and endocrine changes in response to vitamin D supplementation. This will be an impactful area for future research. Animal and human studies point to ovulation as a key to the effects of vitamin D. Lower levels of vitamin D are associated with prolonged time to ovulation or anovulation in both animals and humans (4). However, it is not clear whether these observations stem from alterations at the level of the hypothalamus, the pituitary, or the ovary.

Vitamin D may also influence uterine receptivity and implantation through endometrial gene expression or extravillous trophoblast invasion (5). These pathways highlight the importance of vitamin D during the pre-conception and implantation time frames. Implantation, in turn, is considered an important time window for the future development of pregnancy complications. Clinical trials of vitamin D supplementation for the prevention of pregnancy complications typically enroll women in the late first trimester or during the second trimester. If vitamin D is important for uterine receptivity or embryo implantation, and this is the mechanism for vitamin D's influence on pregnancy complications, then the critical window of exposure to vitamin D will be missed. Thus, future studies should be designed to include pre-conception vitamin D supplementation.

The ideal 25OHD level for reproductive function is unknown and may be higher than existing clinical recommendations. It is possible that vitamin D intake recommendations for women who are trying to conceive or are undergoing fertility treatment should be higher than recommendations based primarily on bone health measures. Higher 25OHD levels, potentially for these brief periods of time, may be warranted if they improve the chances of pregnancy. High levels of 25OHD have been associated with chronic disease, and this is an important consideration when establishing recommendations. This suggests that understanding the 25OHD dose-response association with reproductive endpoints, especially conception, is a critical next step for this research field.

Optimal serum concentrations of 25OHD for health outcomes may vary depending on the health outcome and the population of interest. Further, the required daily intake to achieve the nutrient requirements of a population will differ based on latitude as well as population characteristics, which may change over time. Dietary preferences, food composition, and factors which diminish dermal exposure to ultraviolet light (clothing, sunscreen and melanin) can change over time, in each population. Clinical and national policy recommendations can be refined to meet the needs of specific populations.

Vitamin D supplements are widely available and easy to obtain. Thus, a clinical trial of vitamin D and fertility is feasible. A trial of vitamin D that incorporated both male and female partners and multiple levels of vitamin D supplementation would be important for informing vitamin D recommendations. A trial that collects information on underlying biological pathways could confirm and explain any observed associations. If vitamin D supplementation improves the probability of conception it would be an easily implemented intervention with important consequences for women's and couple's reproductive success.

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