Vitamin D in human reproduction—an evolving landscape

There is a vitamin D deficiency epidemic in the United States that has prompted exploration into many areas of human health and disease. Studies have subsequently linked vitamin D deficiency and insufficiency to many chronic diseases of the cardiovascular and metabolic systems. Given that this steroid hormone has receptors throughout the body including the ovary—in particular the granulosa cells—as well as in the endometrium and placenta, it stands to reason that vitamin D could be impactful on human reproductive success and even obstetrical outcomes.

The data that exist to date on reproductive outcomes are variable. Ozkan et al. evaluated follicular fluid in a prospective manner and correlated vitamin D levels to pregnancy outcomes (1). However, they found a lack of correlation between vitamin D concentration and ovarian response parameters, which suggested that perhaps the endometrium and endometrial receptivity may be the key regulators when it comes to vitamin D and reproductive success. This concept of an endometrial receptivity effect was supported by work from Rudick et al. in an oocyte donation model study (2).

This theory, however, stands in contrast to other studies that have shown that vitamin D status is not impactful on outcomes when a euploid, synchronous ET is performed (3). It is possible that when embryo competence and quality are controlled to the exent possible by achieving an expanded euploid blastocyt for ET, and endometrial synchrony is accounted for, that the impact of vitamin D may not be seen. If these factors are able to be externally controlled, perhaps vitamin D impacts processes involved before the formation of a euploid embryo and may not be limited simply to ovarian response parameters. Indeed, the story may be more complex and may need to take into account dose of bioactive hormone at the receptor site as well as take a closer look at follicular and oocyte paramters—it may be that the follicular maturation process is impacted.

This relationship is quite likely to be influenced by the bioavailability of vitamin D at the target sites. Vitamin D binding protein (VDBP), in the nuclear hormone receptor superfamily, and albumin bind over 99% of the available active hormone, and thus its activity at the receptor is highly dependent upon VDBP concentrations and its polymorphisms, which can vary among ethnicities. When analyzing the direct treatment of granulosa cells by active 1,25-dihydroxyvitamin D3 metabolite, which circumvents and overpowers the VDBP issues, there were changes noted in antimüllerian hormone (AMH) receptor gene expression as well as downstream AMH signaling (4). These data begin to shed light on what has been to date a somewhat limited investigation into the direct effect of vitamin D sufficiency or insufficiency's potential mechanism of action as they pertain to reproductive success.

Thus, the data from Xu et al. are of great interest (5). Through a primate model that has the ability to study follicular maturation from the preantral to antral stage, they show that 1,25-dihydroxyvitamin D3 impacts follicular survival and growth as well as oocyte growth in a dose- and stage-dependent fashion. The in vitro experimental design allowed for control, as well as low- and high-dose 1,25-dihydroxyvitamin D3 exposure. Interestingly, the low dose of 1,25-dihydroxyvitamin D3 impacted preantral follicular survival and a high dose impacted follicular diameter. It is important to note that larger follicular size does not necessarily imply a higher quality follicle or oocyte. Steroid hormones often act along a continuum, and it is possible that supraphysiologic dosing could in fact have diminishing returns or even be toxic.

The fact that Xu et al. demonstrate an effect of vitamin D on ovarian folliculogenesis and do so in a way that demonstrates both a dose- and stage-dependent process may explain some of the disparate findings that surround this steroid's role in reproductive success to date. Prior data present variabilities surrounding the concentration of bioavailable vitamin D as well as the different study endpoints that isolate certain developmental stages. The differential dose effect of 1,25-dihydroxyvitamin D3—with low dose being effective early and high dose being effective later in folliculogenesis—point to a potential vitamin D receptor expression factor, something that has been incompletely included in past analyses. However, given how FSH and LH receptors change in both responsiveness and concentration through the follicular maturation process, this finding fits well into a growing story.

Given the prevalence of vitamin D deficiency, both in the United States and worldwide, the issue of determining a pathophysiologic mechanism as well as clinical impact are important. If its impact on follicular development and downstream oocyte maturation processess such as resumption of meiosis, among others, is further investigated and confirmed, this may have important clinical ramifications as we seek to best take care of the general health of our patients as well as maximize their reproductive outcomes.

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