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LETTER TO THE EDITOR

Is it realistic to consider vitamin D as a follicular and serum marker of human oocyte quality?

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Over the past decade, vitamin D has been spotlighted in many research fields. Nevertheless, numerous publications suggest that its influence on reproductive health is still ambiguous. One of the hypothesis on the importance of vitamin D on the outcomes of Assisted Reproductive Technologies arises from their possible effects on endometrial receptivity and immune-modulating effects.

In Ciepiela et al.'s study, the authors demonstrated that patients with vitamin D < 20 ng/ml in follicular fluid had greater probability of having positive hCG; suggesting that vitamin D in follicular fluid could play a role in oocyte development and embryo quality [1]. Having found no significant differences of serum levels between patients with vitamin D < 20 ng/ml or > 20 ng/ml in terms of age, the number of retrieved oocytes, the number of mature MII oocytes, the number of cycles with no available embryo for embryo transfer, and percentage of top quality embryos, Ciepiela et al.'s results are very interesting. They have found that patients with serum vitamin D deficiency had significantly higher clinical pregnancy rates compared to those with 25(OH)D values exceeding 20 ng/ml (48.2 vs. 25%, $P = 0.001$). However, patients with serum vitamin D deficiency had also significantly higher miscarriage rates (14.5 vs. 3.8%, $P = 0.013$). The difference in the live birth rates between these groups did not reach statistical significance (37.3 vs. 25%, $P = 0.067$).

I have some doubts in the authors' analysis, since they did not consider that bioavailable 25-OH vitamin D is a more robust biomarker than total 25-OH vitamin D [2], and circulating vitamin D metabolites are available to exert biological activity. The majority of circulating vitamin D has high affinity for vitamin D-binding protein (VDBP) with less than 1% of vitamin D circulating as a free form. In addition, the estrogen component, in oral contraceptive pills, may increase VDBP synthesis or decrease its catabolism. Many patients usually take oral contraceptive pills before starting controlled ovarian stimulation; however, these authors did not mention if this was the case for their patients.

Secondly, Ciepiela et al. considered only the sperm concentration as a parameter of semen alteration. However, since men commonly present with a combination of sperm defects, it is necessary to consider, at least, three defects contemporarily. Moreover, defects in morphology can hide genetic abnormalities of the sperm cells [3]. During natural conception, motility of the sperm is highly correlated with its capacity to reach the oocyte. However, to mimic the natural selection characteristics seen in vivo, competent sperm are selected using a (swim-up) motility challenge or a differential gradient [4].

Ciepiela et al., had 78 blastocysts develop from 322 MII stage oocytes. In a previous study [5], on 4.205 cycles, 32.031 MII oocytes were recovered, and 10.925 blastocysts developed. When I consider the total number of embryos obtained in the study of Ciepiela et al., the lower blastocyst rate could be a result of suboptimal semen quality in the population study. Furthermore, the blastocyst rate (%) should be calculated for each patient, as the ratio of the blastocysts developed from fertilized oocytes. In Piccolomini's study, the authors considered a pool of blastocyst, the blastocyst development rate (48.7%) was calculated by dividing the number of blastocysts by the number of fertilized oocytes. In Ciepiela et al., the blastocyst rate should be calculated including the embryos in day three, using a regression model according to Poisson, to reduce the possibility of statistics bias.

Nevertheless, the ability of an oocyte to develop to the blastocyst stage depends on many other factors. Many issues are still unsolved. Is vitamin D, then, affecting

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oocyte quality, embryo quality, and lead the endometrial receptivity? Is ethnicity relevant? Are there any other molecules apart from 25-hydroxy vitamin D and VDBP that should be evaluated as they may have a more relevant role? The truth is that there are still too many unanswered questions today to consider vitamin D as a marker of oocyte quality.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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