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VITAMIN D3 ADMINISTRATION'S THERAPEUTIC BENEFITS ON EMBRYO IMPLANTATION

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Abstract

In vitro fertilization (IVF)-embryo transfer (ET) patients who have embryo implantation issues have been clinically tested for a variety of adjuvants. Vitamin D3, a crucial modulator of many physiological processes, has gained attention as a crucial adjuvant for a successful pregnancy because numerous studies have demonstrated a strong correlation between vitamin D deficiency and implantation failure and fetal growth restriction. Nevertheless, vitamin D has been frequently used in various procedures, producing results that are controversial and not reproducible. In this work, we showed that cyclic intrauterine vitamin D3 delivery enhanced angiogenesis and endometrial receptivity, which may be related to a greater recruitment of natural killer cells that reside in the uterus. Specifically, in vitro, cyclic vitamin D3 therapy strengthened the embryo's adhesion to endometrial cells, indicating that it may be useful in promoting the first maternal-fetal contacts during the early stages of embryo implantation. Our results indicate that vitamin D3 may be used as a risk-free adjuvant before IVF-ET operations to improve the uterine environment and make it favorable for embryo implantation in women who have experienced repeated implantation failure.

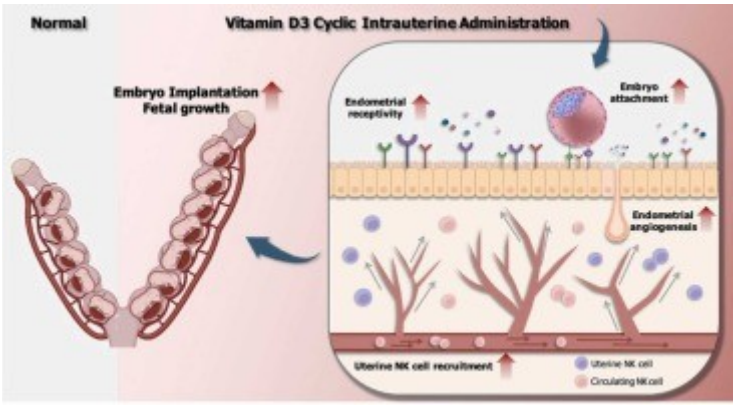
Keywords: Vitamin D3, endometrial receptivity, endometrial angiogenesis,uterine natural killer cells, embryo implantation.

Introduction

In the complex process of embryo implantation, the blastocyst trophectoderm attaches itself to the uterine luminal epithelium, followed by more stable adherence and penetration into the uterine stroma [1], [2]. A vast vascular network that supports the proper growth of the implanted embryo is formed by the decidua, which coordinates this process [3], [4]. Numerous studies have established a robust link between effective pregnancy maintenance and vitamin D status [5, 6, 7]. Vitamin D levels during pregnancy are essential for fetal growth and rise

throughout the first few months of pregnancy and continue to rise until birth [6], [8]. However, there is still uncertainty regarding the precise physiological roles that vitamin D supplementation plays during embryo implantation.

In its active form, cholecalciferol (vitamin D3; 1,25-dihydroxyvitamin D3), vitamin D3 is mainly engaged in the metabolism of calcium and phosphorus, which has a direct bearing on the composition and operation of the skeletal system [9]. By interacting with the vitamin D receptor (VDR), this significantly influences hormone secretion and the immune system [10]. Angiogenesis and re-endothelialization are crucial during embryo implantation and pregnancy, and the vitamin D3–VDR complex stimulates a number of transcription factors that control hypoxia inducible factor 1α signaling [11], [12]. Vitamin D levels in serum and follicular fluid have been found to positively correlate by 6% with the likelihood of a successful pregnancy result after IVF, according to recent research [16], [17], and [18]. Furthermore, enhanced parameters of the regulated ovarian hyperstimulation were substantially correlated with high vitamin D levels [16]. In order to increase implantation rates, we propose an ideal approach for intrauterine vitamin D3 delivery based on our findings.



Material and method

Fertility test

Three groups of female mice were created by random selection and given cyclic treatments every four days for one, two, and twelve days. Certain mice had saline injected into one side of their uterine horns and vitamin D3 put into the other. The mice were put in the same strain of the male cage the following morning. The following morning, the vaginal plug was examined and determined to be on day 1 of pregnancy. Only mice with a vaginal plug were separated from the male at the first day of pregnancy, and the uteri were slaughtered for additional analysis after 17 days. All of the fetus and placenta were weighed, and the number of

implantation sites was noted in order to assess the impact of vitamin D3 on fertility.

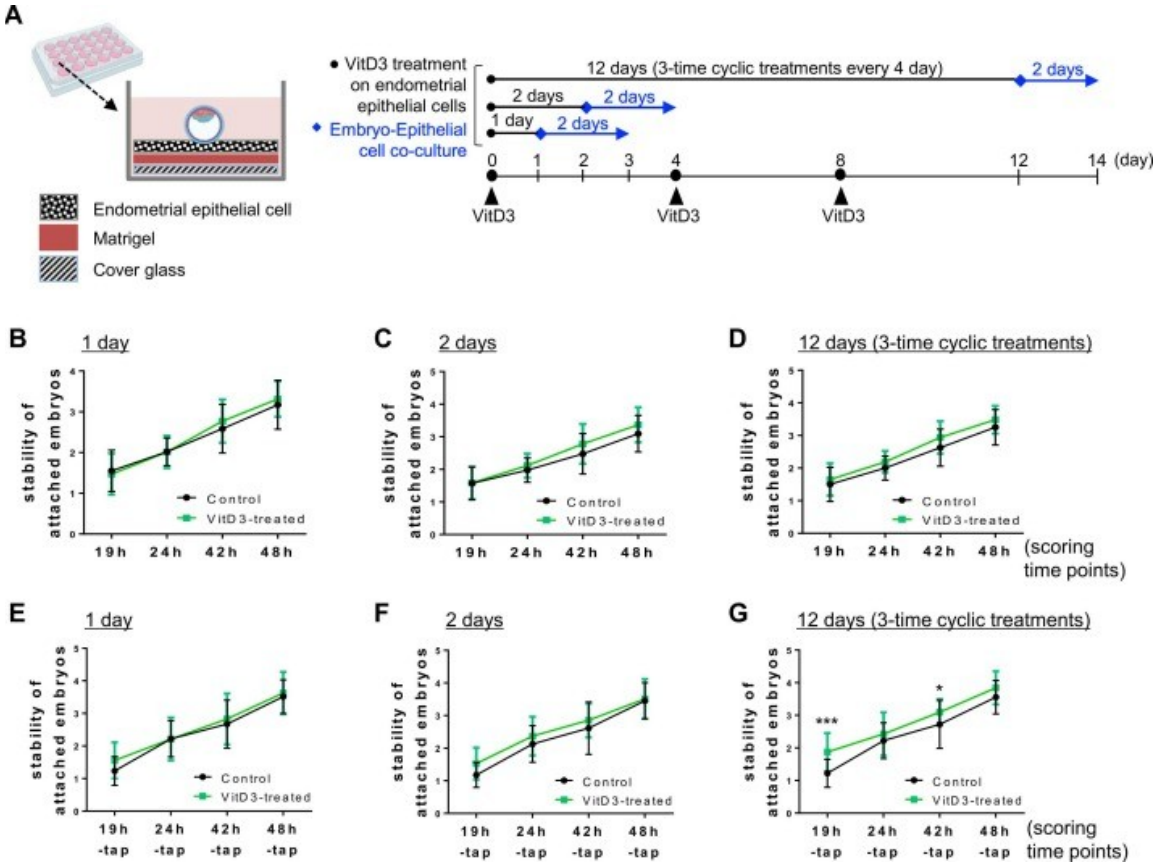


Figure 4: Administration of vitamin D3 accelerates the rate of embryo attachment. (A) 146 embryos (from 14 female mice) were used in the embryo attachment assay experiment. The stability of embryos attached to Ishikawa cells treated with vitamin D3 (y-axis) was measured at the given time-points (x-axis) either with tapping at 1 day (E), 2 days (F), and 12 days (G) or without tapping at 1 day (B), 2 days (C), and 12 days (3-time cyclic treatments every 4 days) (D). (B-G) The unpaired t test is used to examine the data, and p-values (*<0.05, **<0.01, ***<0.001, ****<0.0001) are included.

Discussion

Administration of vitamin D3 accelerates the implantation of embryos.

Using an in vitro model with or without tapping in the presence or absence of vitamin D3 pre-treatment of endometrial cells (1 day, 2 days, and 12 days; three-time cyclic treatments every 4 days), we evaluated the stability of embryos attached onto endometrial epithelial cells in order to assess the effects of vitamin D3 administration on the rate of embryo attachment (Fig. 4A). When the embryos were not disturbed during this procedure, assay studies showed that there was no discernible difference in the stability of connected embryos between the cells prepped with vitamin D3 and those pretreated with saline at any time points. In this

study, we showed that cyclic intrauterine vitamin D3 injection boosted angiogenesis and endometrial receptivity, which in turn attracted more uterine-resident NK cells throughout pregnancy(Fig.4). Specifically, vitamin D3 treatment resulted in a more stable attachment of the embryo to endometrial cells in vitro, indicating that it may be useful in supporting the first maternal-fetal connection during the early phases of embryo implantation.

Our results demonstrated that the group that received vitamin D3 cyclically had the most markedly elevated endometrial expression of adhesion molecules (Itgb3 and Spp1), with particularly high expression in both luminal and glandular epithelia. The group that received only one treatment (1–4 days) showed the greatest variation in the expression of the secretion factor Lif (Fig. 1). Our results showed that cyclic vitamin D3 delivery led to a more stable attachment of embryos on endometrial cells primed with vitamin D3. At day 17 of pregnancy, the group that received three cycles of vitamin D3 therapy also had higher fetal weight and implantation sites. All of these results point to vitamin D3 playing a beneficial function in maternal-fetal interactions when implantation and pregnancy maintenance are just getting started.

Conclusions

Here, we find that cyclic intrauterine vitamin D3 delivery fostered consistent maternal–fetal connections during the early phase of implantation, increased endometrial receptivity and angiogenesis, and triggered the recruitment of uterine-resident NK cells. Based on our results, we propose that vitamin D3 could be used as a risk-free adjuvant during IVF-ET to help women who experience repeated implantation failure.

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