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THE USE OF VITAMIN D IN ASSISTED REPRODUCTIVE TECHNOLOGY PROCEDURES (*ART*) - CAN THE OCCURRENCE OF BREAST CANCER BE REDUCED?

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review paper

Summary

Introduction: Vitamin D has crucial biological activity and antioxidative function involved in human reproduction. Lots of infertility patients worldwide have their children through assisted reproductive technology. Beside endogenous synthesis, it is possible and important to supplement vitamin D with diet. Vitamin D insufficiency is strongly connected with severe diseases, cancers, infertility. Studies have reported vitamin D insufficiency in up to 75% of women with diagnosed breast cancer and improvements in survival after diagnosis in women with higher level of vitamin D.
Aim: The purpose of this narrative review was to elucidate the role of vitamin D in assisted reproductive technology (*ART*) procedures, prevention and reduction of breast cancer incidence providing current evidence from human studies.
Materials and methods: The Medline database was searched using keywords *vitamin D, breast cancer, fertility, supplementation, in vitro fertilization*. The search was made as of April 10, 2023.
Results and discussion: Majority of papers analysed show that vitamin D is important in achieving good quality embryos in procedures of medically assisted reproduction and through effects that are noticeable in endometrium vitamin D supplementation facilitates successful implantation of embryos. Research also shows that there is some elevated risk in developing breast cancer after those procedures, but some papers also show that there is no notable risk, so the results are inconclusive. We found that there is a general agreement that normal serum concentrations of vitamin D acts oncoprotective against breast cancer and may facilitate treatment on already developed cancer.
Conclusion: For women with elevated risk for breast cancer, supplementation with vitamin D after medically assisted reproduction seem to have protective effect.

Keywords: vitamin D, breast cancer, fertility, supplementation, in vitro fertilization

Introduction

Worldwide, infertility affects 123 million women, therefore medically assisted reproductive technology represent important mean to improve fertility rates globally. *In vitro* fertilization with embryo transfer at the end of the procedure is one of the most effective techniques for treating infertility (Tian et al., 2022). Vitamin D is fat-soluble secosteroid which has pivotal role in increasing intestinal absorption of calcium, magnesium and phosphate. Vitamin D is synthesized in the skin from 7-dehydrocholesterol, metabolized within the body to the form $1,25(OH)_2D_3$ and transported by vitamin D-binding protein into the blood (Laganà et al., 2017). The 7-dehydrocholesterol that is produced from cholesterol and stored under the skin, can be converted into vitamin D3 after being exposed to ultraviolet radiation (Wang et al., 2021). Parathyroid hormone, FGF23, calcium and phosphate are the major regulators of the renal 1-hydroxylase (the enzyme producing 1,25(OH)2D), the major enzyme that catabolizes 25(OH)D and 1,25(OH)2D is the 24-hydroxylase (Bikle, 2017). Most actions of 1,25(OH)2D are mediated by the vitamin D receptor (VDR) which is a transcription factor that is coupled with retinoid X receptor that when bound to 1,25(OH)2D regulates gene transcription either positively or negatively (Bikle, 2017). Vitamin D receptor is found in most cells in human body (Bikle, 2017). Along with endogenous synthesis, it is possible and important, in case of insufficiency, to supplement vitamin D with diet. Main sources of vitamin D3 (cholecalciferol) are sea fish fat and cod liver oil, and sources of vitamin D2 (ergocalciferol) are plants and mushrooms (Laganà et al., 2017). The World Health Organization (WHO) defined 'vitamin D insufficiency' as serum level of 25OHD below 20 ng/ml (50 nmol/L) (Skowrońska et al., 2016). Fat-soluble vitamins have crucial biological activity, antioxidative function involved in, for example, human reproduction. There are association between levels of fat-soluble vitamin in follicular fluid, quality of oocytes and consequently embryo development (Skowrońska et al., 2020). Vitamin D plays an important role in maintaining the normal development of the uterus and ovaries, 25(OH)D levels have a significant impact on the

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fertility, which suggest that 25(OH)D may affect the fertility of patients with infertility (Tian et al., 2022). Paffoni et al. (2014) concluded that vitamin D insufficiency negatively affects clinical pregnancy rate in women undergoing *in vitro* fertilization (*IVF*) procedure. In male infertility, insufficiency or high level of vitamin D in serum have negative impact on spermatozoa number, their progressive motility and sperm morphology (Nikolac Gabaj et al., 2020). Vitamin D insufficiency is strongly connected with severe diseases pointing out cancers and pregnancy complications including infertility. Studies have reported vitamin D insufficiency in up to 75% of women with diagnosed breast cancer and improvements in survival after diagnosis in women with higher level of vitamin D. It affects approx. 200 genes connected with cellular proliferation, apoptosis and terminal differentiation of normal and cancer cells. Vitamin D receptors have been found in up to 80% of breast cancers (Hines et al., 2010).

The purpose of this review was to elucidate the role of vitamin D in assisted reproductive technology procedures, prevention and reduction of breast cancer incidence providing current evidence from human studies.

Materials and methods

The Medline database was searched using keywords *vitamin D, breast cancer, fertility, supplementation, in vitro fertilization*. The search was made up to April 20, 2023. After the extraction of all papers, they were compared to each other for duplicates and related studies, so two authors separately analysed the inclusion of studies according to the set criteria. We analysed 18 papers that included 14 reviews, 2 clinical trials and 2 randomized controlled trials. Results are shown in form of narrative review.

Results and discussion

Role of vitamin D in medically assisted reproduction

Vitamin supplementation is present worldwide as a form of preparation for pregnancy or IVF procedures and vitamin D is an important part. When analysing publications, we found confirmation that this vitamin plays an important part for oocyte and embryo quality. Polycystic ovary syndrome patients are characterized with insulin resistance, metabolic and reproductive functions that make achieving pregnancy difficult and often seek fertility counselling or require fertility procedures, they are sometimes deficient in vitamins such as vitamin D, chromium and omega-3 (Fagfoori et al., 2017). Ozyurt and Karakus (2022) show that both serum and FF 25-hydroxyvitamin D level of women with PCOS at the time of oocyte retrieval are like non-PCOS controls and that follicular fluid 25-hydroxyvitamin D levels correlate with total and MII oocyte counts, positive pregnancy test and clinical pregnancy rate but do not correlate with miscarriage and live birth rates. Paffoni et al. (2014) recruited 154 women with serum 25(OH)D <20 ng/mL and 181 women with serum 25(OH)D ≥20 ng/mL and found that clinical pregnancy rates were 20% (30/154) and 31% (56/181 and subgroup analyses showed that the group of women with the highest serum levels (>30 ng/mL) had the highest chances of pregnancy. Vitamin D influences embryo cleavage and implantation in patients with repeated implantation failure by affecting the expression pattern and regulatory modifications of the progesterone receptors in the endometrial stromal cells (Hosseinirad et al., 2020).

Kermack et al. (2020) showed that increased dietary intake of omega-3 fatty acids, vitamin D, and olive oil for 6 weeks before in vitro fertilization (IVF) or IVF–intracytoplasmic sperm injection (ICSI) altered the rate of embryo cleavage. Possible explanation is that vitamin D alters AMH signalling, FSH sensitivity, and progesterone production and release in human granulosa cells, indicating a possible physiologic role for vitamin D in ovarian follicular development (Irani and Merhi, 2014). Not only that vitamin D influences embryo quality, but vitamin D supplementation regulates local immune response of natural killer cells for optimization of maternal tolerance for implantation in women with repeated implantation failure (Chen et al, 2020).

Vitamin D is also having an impact on cycles with donated oocyes and recipients with nonreplete vitamin D status [25(OH)D<30 ng/mL] were associated with lower pregnancy rates suggesting that the effects of vitamin D may be mediated through the endometrium (Rudick et al., 2014).

Grzechocinska et al. (2013) conclude that results in patients without calciferol insufficiency are explained by reports about high concentration of vitamin D and its metabolites in human in decidua collected in the 1st trimester of pregnancy which suggests its contribution in proper implantation and local immunological preference of the embryo.

There are some papers that haven not found a positive link between vitamin D levels and fertilization success or embryo development (Skowronska et al., 2020) and that neither free nor total 25(OH) vitamin D seems to play a major role in human embryo implantation (Tian et al., 2022).

Vitamin D is also important in sperm quality and male fertility. The vitamin D receptor and the vitamin D inactivating enzyme CYP24A1 are co-expressed in

high quality sperm and research results provide proof of principle for a CYP24A1-based sperm test to improve fertility outcome for infertile patients referred for IUI and supports a role for vitamin D metabolites during fertilization (Hansen et al., 2019).
Vitamin D serum concentrations depend not only on supplementation but on environmental factors. There were significant differences in 25-hydroxyvitamin D (25(OH)D) concentrations in different seasons and vitamin D deficiencies are lowest in summer when levels of vitamin D are highest due to sunlight exposure and these vitamin D concentrations significantly correlated with female infertility (Wang et al., 2021). Rogenhofer et al. (2022) show that highest anti Muller hormone concentrations were found between August and October when vitamin D has highest concentrations. Research of Aerfi et al. (2018) showed that concealing dress code is an independent risk factor for vitamin D deficiency due to a lack of skin exposure to sunlight and it may play a crucial role in reduced ovarian reserve in infertile female Iranian population.

Link between breast cancer and medically assisted reproduction

Medically assisted reproduction includes the use of gonadotropins, clomiphene citrate or letrozole as inductors of ovulation and these medications can influence estrogene levels in female body. Breast cancer is sensitive on estrogene levels and there is a concern that ovarian stimulation may alter the risk of developing breast cancer after such treatments. Some research show that women who received six or more IVF cycles did not have an increased risk of breast cancer, there was no excess breast-cancer risk associated with clomiphene, human chorionic gonadotropin, gonadotropin analogues and progesterone and there was no significant association between fertility treatment and excess breast-cancer risk in patients with more than 10 years' follow-up (Cullinane et al., 2022). Also, there was no significant increase in the risk of breast cancer among women treated with any ovarian stimulation drug for infertility compared with that in unexposed controls from the general population and the infertile population (Beebeejaun et al., 2021). Among women undergoing fertility treatment in the Netherlands between 1980 and 1995, IVF treatment compared with non-IVF treatment was not associated with increased risk of breast cancer after a median follow-up of 21 years (Belt-Dousebout et al., 2016). Gronwald et al. (2016) show that there was no significant relationship between the use of any fertility medication or IVF and the subsequent risk of ovarian cancer among women with a BRCA mutation.
In contrast some research shows that there is a positive link between fertility treatment and risk of breast cancer. Age 40 or more at IVF treatment, hormonal infertility and 4 or more IVF cycles were found to be risk factors to develop breast cancer compared to the general population and 29% of women in IVF treatments had positive family history of breast cancer (Pappo et al., 2008). Women exposed to ART had an elevated risk of breast and research findings show increased risk in the study population warrant continued monitoring of women treated with ART as this population advances into more typical cancer age ranges (Reigstad et al., 2015).
Women who have been exposed to fertility drugs with IVF seem to have a transient increase in the risk of having breast or uterine cancer diagnosed in the first year after treatment, though the incidence overall is no greater than expected and unexplained infertility was associated with an increased risk of a diagnosis of ovarian or uterine cancer (Venn et al., 1999).
In a review paper Impicciatore and Tiboni (2006) report an increased risk was recently observed in women giving birth after in vitro fertilization (IVF), but it appeared to be consequential to the infertile status rather than the effect of fertility drugs and there is a possible trend towards an increased risk has been reported by some authors for endometrial cancer. Kessous et al. (2016) show that patients with a history of IVF treatments had a significantly increased risk of being diagnosed with ovarian and uterine cancer, but a history of IVF treatment remained independently associated with ovarian and uterine cancer.

Role of vitamin D supplementation in breast cancer

When analysing papers on relationship between vitamin D concentrations we found that vitamin D has mostly anticancerogenic properties in relation to breast cancer. Some studies strongly suggest that vitamin D deficiency increases the risk of developing cancer and that avoiding deficiency and adding vitamin D supplements might be an economical and safe way to reduce cancer incidence and improve cancer prognosis and outcome (Feldman et al., 2014). Preclinical data have indicated that vitamin D affects up to 200 genes that influence cellular proliferation, apoptosis, angiogenesis, terminal differentiation of normal and cancer cells and that vitamin D receptors have been found in up to 80% of breast cancers influencing patient survival (Hines et al., 2010).
Among premenopausal women, high intake of low-fat dairy foods containing vitamin D as a component was associated with reduced risk of breast cancer (Shin et al., 2002).

Women with serum 25(OH)D levels less than 20 ng/ml and calcium levels less than 10.5 mg/dl had higher odds of having breast cancer (Sofi et al., 2018) and vitamin D supplements appear protective against breast cancer development (Rossi et al., 2014).

Merchan et al. (2018) conclude that vitamin D and its receptor show oncoprotective actions and vitamin D presents oncoprotective actions through modulation of inflammation, cell proliferation, cell differentiation, angiogenesis, invasive and metastatic potential, apoptosis, miRNA expression regulation and modulation of the Hedgehog signalling pathway.

25(OH)D deficiency was directly related to breast cancer incidence while total vitamin D and supplemental vitamin D intakes had an inverse relationship with this outcome (Hossain et al, 2019). In another study the combination of ω-3 free fatty acids (ω-3 FFAs) and 1α, 25-dihydroxy-vitamin D dramatically enhances cell apoptosis among three subtypes of breast cancer cell lines (Yang et al., 2017).

Vitamin D may inhibit the transformation of normal mammary progenitors into breast cancer stem cells that initiate and sustain the growth of breast tumours through modulation of long chain RNAs that are important for breast cancer pathogenesis (Blasiak et al., 2022).

Conclusions

Women with elevated risk for developing breast cancer going through medically assisted reproduction, could benefit from supplementation with vitamin D to reduce the risk of developing breast cancer.

References

Arefi, S., Khalili, G., Iranmanesh, H., Farifteh, F., Hosseini, A., Fatemi, H.M., Lawrenz, B. (2018): Is the ovarian reserve influenced by vitamin D deficiency and the dress code in an infertile Iranian population? *J Ovarian Res.* 11(1), 62.

Bandera Merchan, B., Morcillo, S., Martin-Nuñez, G., Tinahones, F.J., Macías-González, M. (2017): The role of vitamin D and VDR in carcinogenesis: Through epidemiology and basic sciences. *J Steroid Biochem Mol Biol.* 167, 203-218.

Beebeejaun, Y., Athithan, A., Copeland, T.P., Kamath, M.S., Sarris, I., Sunkara, S.K. (2021): Risk of breast cancer in women treated with ovarian stimulation drugs for infertility: a systematic review and meta-analysis. *Fertil Steril.* 116 (1), 198-207.

Bikle, D.D. (2017): Vitamin D: Production, Metabolism, and Mechanisms of Action. [Updated 2021 Dec 31]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278935/

Blasiak, J., Chojnacki, J., Pawlowska, E., Jablkowska, A., Chojnacki, C. (2022): Vitamin D May Protect against Breast Cancer through the Regulation of Long Noncoding RNAs by VDR Signaling. *Int J Mol Sci.* 23 (6), 3189.

Chen, X., Diao, L., Lian, R., Qi, L., Yu, S., Liu, S., Lin, S., Xue, Z., Zeng, Y. (2020): Potential impact of maternal vitamin D status on peripheral blood and endometrium cellular immunity in women with recurrent implantation failure. *Am J Reprod Immunol.* 84 (1), e13243.

Cullinane, C., Gillan, H., Geraghty, J., Evoy, D., Rothwell, J., McCartan, D., McDermott, E.W., Prichard, R.S. (2022): Fertility treatment and breast-cancer incidence: meta-analysis. *BJS Open.* 6 (1), zrab149.

Faghfoori, Z., Fazelian, S., Shadnoush, M., Goodarzi, R. (2017): Nutritional management in women with polycystic ovary syndrome: A review study. *Diabetes Metab Syndr.* 11 Suppl 1, S429-S432.

Feldman, D., Krishnan, A.V., Swami, S., Giovannucci, E., Feldman, B.J. (2014): The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer.* 14 (5), 342-357.

Gronwald, J., Glass, K., Rosen, B., Karlan, B., Tung, N., Neuhausen, S.L., Moller, P., Ainsworth, P., Sun, P., Narod, S.A., Lubinski, J., Kotsopoulos, J., Lynch, H.T., Cybulski, C., Kim-Sing, C., Friedman, S., Senter, L., Weitzel, J., Singer, C., Eng, C. (2016): Treatment of infertility does not increase the risk of ovarian cancer among women with a BRCA1 or BRCA2 mutation. *Fertil Steril.* 105 (3), 781-785.

Grzechocinska, B., Dabrowski, F.A., Cyganek, A., Wielgos, M. (2013): The role of vitamin D in impaired fertility treatment. *Neuro Endocrinol Lett.* 34 (8), 756-762.

Hansen, L., Lorenzen, M., Bentin-Ley, U., Nielsen, J., Krog, H., Berg, A.H., Bonnie Sofie Håkansson, Astrid Munk Pedersen, T. Høst, Juul, A., Bach Jensen, M. (2019): Presence of the vitamin D inactivating enzyme CYP24A1 in human sperm and prediction of the success of intrauterine insemination: A prospective study. *J Steroid Biochem Mol Biol.* 191, 105353.

Hines, S.L., Jorn, H.K.S., Thompson, K.M., Larson, J.M. (2010): Breast cancer survivors and vitamin D: A review. *Nutrition* 26 (3), 255-262.

Hossain, S., Beydoun, M.A., Beydoun, H.A., Chen, X., Zonderman, A.B., Wood, R.J. (2019): Vitamin D and breast cancer: A systematic review and meta-analysis of observational studies. *Clin Nutr ESPEN.* 30, 170-184.

Hosseinirad, H., Novin, M., G., Hosseini, S., Nazarian, H., Amidi, F., Paktinat, S., Azizi, E., Mofarahe, Z., S. (2020): Effect of 1,25(OH)2-vitamin D3 on expression and phosphorylation of progesterone receptor in cultured endometrial stromal cells of patients with repeated implantation failure. *Acta Histochem.* 122 (2), 151489.

Impicciatore, G.G., Tiboni, G.M. (2011): Ovulation inducing agents and cancer risk: review of literature. *Curr Drug Saf.* 6 (4), 250-258.

Irani, M., Merhi, Z. (2014): Role of vitamin D in ovarian physiology and its implication in reproduction: a systematic review. *Fertil Steril.* 102 (2), 460-468.e3.

Kermack, A.J., Lowen, P., Wellstead, S.J., Fisk, H.L., Montag, M., Cheong, Y., Osmond, C., Houghton, F.D., Calder, P.C., Macklon, N.S. (2020): Effect of a 6-week 'Mediterranean' dietary intervention on in vitro human embryo development: the Preconception Dietary Supplements in Assisted Reproduction double-blinded randomized controlled trial. *Fertil Steril.* 113 (2), 260-269.

Kessous, R., Davidson, E., Meirovitz, M., Sergienko, R., Sheiner, E. (2016): The risk of female malignancies after fertility treatments: a cohort study with 25-year follow-up. *J Cancer Res Clin Oncol.* 142 (1), 287-293.

Laganà, A.S., Vitale, S.G., Ban Frangež, H., Vrtačnik-Bokal, E., D'Anna, R. (2017): Vitamin D in human reproduction: the more, the better? An evidence-based critical appraisal. *Eur Rev Med Pharmacol Sci.* 21 (18), 4243-4251.

Nikolac Gabaj, N., Unic, A., Miler, M., Pavicic, T., Culej, J., Bolanca, I., Herman Mahecic, D., Milevoj Kopcinovic, L., Vrtaric, A. (2020): In sickness and in health: pivotal role of vitamin D. *Biochem Med (Zagreb).* 30 (2), 020501.

Ozyurt, R., Karakus. C. (2022): Follicular fluid 25-hydroxyvitamin D levels determine fertility outcome in patients with polycystic ovary syndrome. *Taiwan J Obstet Gynecol.* 61 (4), 620-625.

Paffoni, A., Ferrari, S., Viganò, P., Pagliardini, L., Papaleo, E., Candiani, M., Tirelli, A., Fedele, L., Somigliana, E. (2014): Vitamin D Deficiency and Infertility: Insights From in vitro Fertilization Cycles. *J Clin Endocrinol Metab.* 99 (11), E2372- E2376.

Paffoni, A., Somigliana, E., Sarais, V., Ferrari, S., Reschini, M., Makieva, S., Papaleo, E., Viganò, P. (2019): Effect of vitamin D supplementation on assisted reproduction technology (ART) outcomes and underlying biological mechanisms: protocol of a randomized clinical controlled trial. The 'supplementation of vitamin D and reproductive outcome' (SUNDRO) study. *BMC Pregnancy Childbirth.* 19 (1), 395.

Pappo, I., Lerner-Geva, L., Halevy, A., Olmer, L., Friedler, S., Raziel, A., Schachter, M., Ron-El, R. (2008): The possible association between IVF and breast cancer incidence. *Ann Surg Oncol.* 15 (4), 1048-1055.

Reigstad, M.M., Larsen, I.K., Myklebust, T.Å., Robsahm, T.E., Oldereid, N.B., Omland, A.K., Vangen, S., Brinton, L.A., Storeng, R. (2015): Risk of breast cancer following fertility treatment-A registry based cohort study of parous women in Norway. *Int J Cancer.* 136 (5), 1140-1148.

Rogenhofer, N., Jeschke, U., von Schönfeldt, V., Mahner, S., Thaler, C.J. (2022): Seasonal dynamic of cholecalciferol (D3) and anti-Muellerian hormone (AMH) with impact on ovarian response and IVF/ICSI. *Arch Gynecol Obstet.* 306 (1), 219–228.

Rosato, V., Bertuccio, P., Bosetti, C., Negri, E., Gross, N.D., Ferraroni, M., Decarli, A., Talamini, R., Dal Maso, L., Falcini, F., Montella, M., Franceschi, S., La Vecchiam C. (2013): Nutritional factors, physical activity, and breast cancer by hormonal receptor status. *Breast.* 22 (5), 887-893.

Rossi, R.E., Pericleous, M., Mandair, D., Whyand, T., Caplin, M.E. (2014): The role of dietary factors in prevention and progression of breast cancer. *Anticancer Res.* 34 (12), 6861-6875.

Rudick, B.J., Ingles, S.A., Chung, K., Stanczyk, F.Z., Paulson, R.J., Bendikson, K.A. (2014): Influence of vitamin D levels on *in vitro* fertilization outcomes in donor-recipient cycles. *Fertil Steril.* 101 (2), 447-452.

Shin, M.-H., Holmes, M.D., Hankinson, S.E., Wu, K., Colditz, G.A., Willett, W.C. (2002): Intake of Dairy Products, Calcium, and Vitamin D and Risk of Breast Cancer. *J Natl Cancer Inst.* 94 (17), 1301-1311.

Skowrońska, P., Kunicki, M., Pastuszek, E., Konieczna, L., Bączek, T., Łukaszuk, K. (2020): Follicular fat-soluble vitamins as markers of oocyte competency. *Syst Biol Reprod Med.* 66 (2), 112-121.

Skowrońska, P., Pastuszek, E., Kuczyński, W., Jaszczoł, M., Kuć, P., Jakiel, G., Wocławek-Potocka, I., Łukaszuk, K. (2016): The role of vitamin D in reproductive dysfunction in women – a systematic review. *Ann Agric Environ Med*. 23(4), 671-676.

Sofi, N.Y., Jain, M., Kapil, U., Seenu, V., R., L., Yadav, C.P., Pandey, R.M., Sareen, N. (2018): Reproductive factors, nutritional status and serum 25(OH)D levels in women with breast cancer: A case control study. *J Steroid Biochem Mol Biol.* 175, 200-204.

Tian, M., Zeng, S., Cai, S., Reichetzeder, C., Zhang, X., Yin, C., Kuang, W., Cheng, K., Jiang, Y., Tao, M., Zeng, Y., Lin, G., Li, J., Gong, F., Hocher, B. (2022): 25(OH)VitD and human endocrine and functional fertility parameters in women undergoing IVF/ICSI. *Front. Endocrinol.* 13, 986848.

van den Belt-Dusebout, A.W., Spaan, M., Lambalk, C.B., Kortman, M., Laven, J.S.E., van Santbrink, E.J.P., van der Westerlaken, L.A.J., Cohlen, B.J., Braat, D.D.M., Smeenk, J.M.J., Land, J.A., Goddijn, M., van Golde, R.J.T., van Rumste, M.M., Schats, R., Józwiak, K., Hauptmann, M., Rookus, M.A., Burger, C.W., van Leeuwen, F.E. (2016): Ovarian Stimulation for In Vitro Fertilization and Long-term Risk of Breast Cancer. *JAMA.* 316 (3), 300-312.

Venn, A., Watson, L., Bruinsma, F., Giles, G., Healy, D. (1999): Risk of cancer after use of fertility drugs with in-vitro fertilisation. *Lancet.* 354 (9190), 1586-1590.

Wang, X., Zhao, S., Zhou, M., Jiang, L. (2021): Factors influencing vitamin D levels in women attending the fertility clinic and the effect on assisted fertility outcomes. *Ann Palliat Med.* 10 (7), 7813-7822.

Yang, J., Zhu, S., Lin, G., Song, C., He, Z. (2017): Vitamin D enhances omega-3 polyunsaturated fatty acids-induced apoptosis in breast cancer cells. *Cell Biol Int.* 41 (8), 890-897.