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Review Article

ROLE OF VITAMIN D ON ANTI-MULLERIAN HORMONE (AMH) AND POLYMORPHISM OF AMHR II IN INFERTILITY: A REVIEW

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ABSTRACT

Deficiency of vitamin D_3 has become common in both developed and developing countries. Vitamin D receptors are found on the granulosa cells of ovarian tissue and its deficiency plays a role in ovarian dysfunction. Anti Mullerian Hormone (AMH) is generated in the small and growing follicles of ovaries by the granulosa cells. Serum AMH is one of the marker for ovarian reserve. We reviewed the current literature on Vitamin D3 and AMH in present clinical practice. There is a relationship between vitamin D_3 and Anti-Mullerian Hormone, which exists at serum as well as genetic level. The AMH gene promoter has vitamin-D responsive elements, which gives the research-based evidence that AMH gene expression is effected by Vitamin D_3. This systematical review is done to assess and encapsulate the available proof concerning the correlation between vitamin D_3 and AMH and its type II receptor (AMHR II) functioning.

Keywords: AMHR II, Anti-mullerian hormone, Granulosa cells, Infertility, Polymorphism, Vitamin D

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INTRODUCTION

Infertility is an expanding health problem seen in both developing and developed countries. The hormone Vitamin D_3 is generated by the skin when it is exposed to sunlight and below 20% is supplied by dietary sources [1]. Liver produces Hydroxyvitamin D (25OH-D) by the transformation of vitamin D by the action of 25-hydroxylase. The active form, 1,25-dihydroxyvitamin D_3 is made in the kidneys by the activity of 1a-hydroxylase (fig. 1) [2]. The production of an active form of vitamin D not only occurs in kidneys but also in different tissues like the breast, brain, ovaries, colon and prostrate by 1α-hydroxylase activity [3].

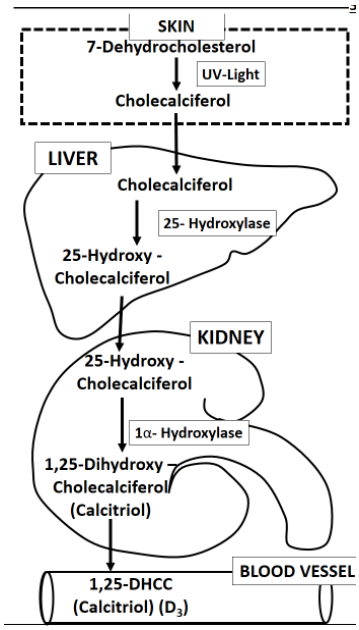

Fig. 1: Activation of vitamin D3

Receptors of vitamin D (VDR) are seen in different parts of the body, such as the intestines, parathyroid glands and skeleton as well as present in the organs of reproduction such as the uterus, ovaries, placenta, testes, pituitary and hypothalamus [4]. There are studies on both animals and humans that put forward the role of vitamin D_3 in the reproductive physiology of females [5]. Deficiency of dietary vitamin D_3 outcomes in a reduction of complete fertility in rats by 75%, along with a 30% fall in dimensions and impairment in infant growth [6]. The *in vitro* therapy of vitamin D_3 on ovarian cells enhanced the proffering of the gonadal hormones, estrogen, progesterone and estrone [7, 8]. A study suggests that, vitamin D_3 insufficiency is related with numerous expressions of PCOS

(Polycystic Ovarian Syndrome) involving anovulatin, insulin resistance as well as hyperandrogenism [9]. Supplementation of Vitamin D_3 has improved the menstrual cycle, hyperandrogenism and other metabolic aspects of PCOS, showing a direct positive outcome of vitamin D_3 on feritility in females [10]. Vitamin D_3 binds to vitamin D receptor and acts as a transcription factor. Vitamin D responsive elements are identified in AMH promoter region and AMH mRNA expression is over-expressed concerning to vitamin D_3 [11]. As vitamin D activity is mediated by VDR, investigation of the VDR genetic variation may explain the character of vitamin D in PCOS. Polymorphism of VDR may contribute to PCOS susceptibility [12].

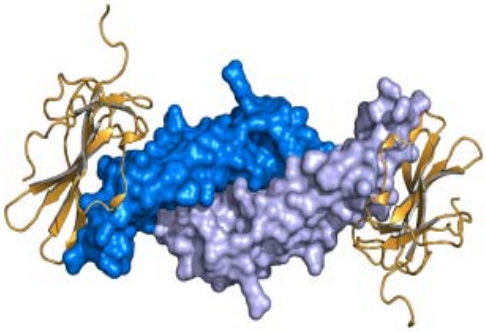

Fig. 2: Structure of AMH and AMHR II

Alfred Jost, a French Endocrinologist, has explored the AMH (Anti Mullerian Hormone) (fig. 2) [13] or Mullerian Inhibiting Hormone (MIH). In females, granulosa cells of ovaries produces AMH and in males by Sertoli cells of the testis. As a biomarker, it plays a vital role in folliculogenesis [14]. The gene that codes for AMH is present on the short arm of chromosome 19, and it is coded between the regions p13.2 and p13.3, which is divided among five exons and has 275 base pairs (bp) [15]. AMH is a member of the transforming growth factor-beta superfamily [16]. The hormone AMH is responsible for the lapse of Paramesonephric ducts in vertebrates as well as in male bird embryos [17]. In female fetuses, the production of AMH begins after 36 w of gestation, which is produced solely in the ovarian follicles by the granulosa cells and is not dependable on gonadotropins [18]. When the follicles are taken on from primordial cells to convert to the primary follicle stage, AMH secretions begins and its secretions summit at the pre-antral stage and decline as they outstretch to the terminal stage whose distinct state makes itself accessible for election by FSH (follicle-stimulating hormone)[16]. There is no significant change establish in AMH levels in pregnancy, as estradiol and FSH levels doesn't change during gestation. Consequently, FSH does not actively contribute in AMH synthesis and its secretion [19]. In the past few years, studies have revealed that serum AMH levels throw back the size of the primordial follicle pool, which agree firmly with the number of antral follicles and manifest depletion throughout reproductive life [20, 21]. So, AMH perhaps is a good marker for the women who encounter *in vitro* fertilization (IVF) treatment, as it reflects ovarian aging [22].

AMH attaches to Type I receptors shared with the bone morphogenetic protein (BMP) pathway (ACVR 1 and BMPR1A) and its solitary Type II receptor AMHR II (Anti Mullerian Hormone Type II Receptor) in the Mullerian duct mesenchyme, which operates the AMH signaling pathway and initiating lapse of Mullerian Ducts [23]. The AMHR II receptor manifest in the ovary right away after birth and carry on to be expressed throughout life [24]. The AMHR II receptor is there in the testes (sertoli and Leydig cells) and in the ovaries (theca and granulosa cells) [25]; they are also present in the prostate [26], endometrium [27], and also present in the ductal epithelium of mammary gland [28]. The AMHR-II has also proved to be in several cancer cell lines such as the cervical, endometrial, epithelium of ovaries and breast [15]. The absence of functional AMH or its receptor (AMHR II) consequences in an infrequent recessive disorder known as Persistent Mullerian Duct Syndrome (PMDS) that is identified by the presence of Mullerian duct-derived tissues, including oviducts, uterus and vagina in a fully virilized male [29]. The serum concentration of AMH is suggested in predicting the victory of assisted reproductive technologies (ART) [30]. The AMH is an essential ligand-based receptor type-II (AMHR-II), that it inhibits other Transforming growth factors-β (TGF-β) family members to share its receptor [31].

Recent studies have showed that there is an affiliation of the polymorphisms of AMH and its receptor AMHR II with estradiol levels in menstrual cycle throughout its early follicular phase, which submits a character of AMH in the regulation of susceptibility of FSH [32]. We aim to investigate the genetical malformations in the AMH and its receptor AMHR II genes may show its effect on hormonal function in folliculogenesis, giving rise to infertility. The outcome of this review was to relate the association of Vitamin D3 and AMH with the polymorphism of AMHR II in infertility. We evaluated the current literature for the use of AMH in assessing the ovarian reserve and polymorphism of AMHR II related to infertility.

Search strategy

A methodical review of the literature was performed in Research Gate, Google Scholar, Web of Science, Embase and PubMed central reporting in English to assess the correlation connecting vitamin D_3 and the AMH on polymorphism of AMHR II (fig. 3). The keywords used in the search were "AMH and Vit D_3", AMH and polymorphism of AMHR II, "Vit D_3 and polymorphism of AMHR II", "AMH and Infertility", "Vit D_3 and Infertility", "AMH, Vit D_3 and AMHR II". About 2052 articles were found. These articles were then assessed for relevance and quality and 21 of these studies were included as a part of this review.

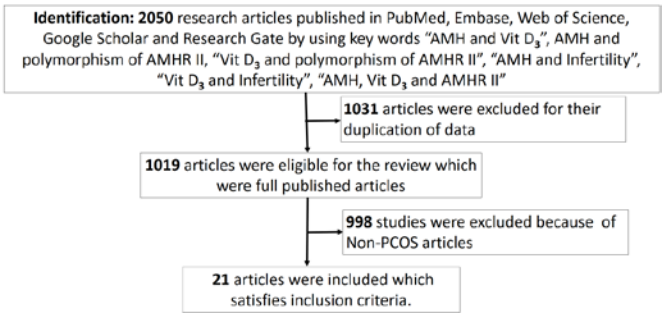

Fig. 3: Sample size flow chart using PRISMA for review

Inclusion and exclusion criteria

Prospective studies and retrospective studies involving AMH, Vit D_3, AMHR II and Infertility. Studies that did not include AMH and Vitamin D_3 and women who are suffering from disorders other than PCOS are excluded.

DISCUSSION

Vitamin D_3 plays a dominant role in reproduction and there are many clinical studies that put forward a correlation between sufficient serum vitamin D_3 levels and improved fertility rate in women with infertility [33]. Vitamin D_3 may influence ovarian

function and AMH production [34]. Few researchers have noticed a direct relationship between vitamin D_3 and AMH [35]. It is considered that sudden increased intake of excess vitamin D_3 progressively elevates serum AMH in young women of reproductive age [36].

AMH prevents the transition of the primordial follicle to the primary follicle. The inhibitory effects on granulosa cell differentiation is mediated by highly specific AMHR-II; thus, higher AMH is accountable for suppressing the maturation of follicles. Vitamin D_3 plays a role in inhibiting AMHR-II [37]. Malloy *et al.*, conducted few studies which showed that AMH promoter has a functional vitamin D_3 response element (VDRE), whose expression is controlled by $1,25(OH)_2D_3$ [38]. Mostly, the specified genes were represented by AMH action. All of AMHR-II-482 A>G genotype alterations involves a decrease in the ovarian reserve. AMHR-II-482 A>G genotype alterations also involved in ISV 5-6 G>T genotype alterations. In women who conceive naturally, homozygote mutations were seen in all SNPs.-482 A>G genotype alterations were seen in two patients with repeated pregnancy loss (RPL) and one case of fetal growth restriction (FGR) [39]. Study done by Yoko Yoshida *et al.* in Japanese women has indicated the participation of AMHRII-482 A>G polymorphism on the breakdown of follicular development [39]. The association of the AMH 146 T> G (rs10407002) polymorphism and the GG genotype may lower the chance of getting pregnant with IVF when compared with others [40].

In recent years' study done by Andersen CY *et al.*, put forward that the fall in control of AMH action is by the FSH through estradiol production because of the antagonistic relation of AMH to estradiol concentration or hindrance of AMH, which suppresses the AMH synthesis by FSH and mostly by estradiol [41]. Few studies stated that, among bearer of AMH polymorphism, the fundamental levels of FSH happen to be less when compared to previous IVF attempts and conception was scientifically more with greater estradiol levels in blood below 1500pg/ml, and within the non-bearer of AMHR-II polymorphism, follicular count was more in women who underwent more than couple of IVF trials and the entire amount of gonadotropic hormones was less in women with greater estradiol levels in blood above 1500pg/ml. AMH and AMHR-II SNPs influence the expressway of AMH, that leads towards the quickened follicular assignment, which results in FSH threshold variation individually [41]. The evaluation of AMH and AMHR II SNP's along with FSHR SNP's and ESR1 SNPs which, come up with the forecast of ovarian response in women planning for IVF [42]. In another study, the hereditary variants of AMH and AMHR-II genes may be correlated with infertility, suggesting their part in the pathophysiology of normo-estrogenic and normo-ovulatory infertility [43].

The scrutiny of DNA methylation suggested that, the methylation of AMHR II and INSR genes was associated with characteristics of PCOS and insulin resistance in PCOS. The pathogenesis of PCOS is associated with the methylation levels of AMHR II and INSR genes [44]. Shan-Jie Zhou *et al.* in their study on the comparison of ovarian reserve between fertile and infertile healthy Chinese women of reproductive age found that there was uniformity in ovarian reserve when compared between fertile and infertile women, and there was no correlation with infertility. The diminished ovarian reserve represents a manifestation of aging [45].

CONCLUSION

This review summarizes the measurement of serum AMH as a proper marker for ovarian reserve. This new knowledge on AMH could guide the clinicians for new hormonal therapies and could improve the *in vitro* procedure of human oocyte maturation. Thus, AMH treatments in infertility has a potential to improve IVF treatment. The only limitation of our study was a review; more meta-analysis is warranted.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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