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The association of vitamin D with semen quality and fertility hormones in idiopathic recurrent pregnancy loss without the female factor

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Abstract

Background/Aim: There is a lack of data about male contribution to idiopathic recurrent pregnancy loss (IRPL). The study aimed to investigate the factors associated with males, including Vitamin D, semen parameters, fertility hormones, and some demographical features in IRPL.
Methods: In this cross-sectional study, the data of 41 men whose partners were diagnosed with recurrent pregnancy loss between February 2014 to February 2015 were collected. Female partners were examined fully, including thrombophilia factors, and no cause was detected. The karyotypes of both partners were normal. Men's 25-hydroxy-vitamin D (25-OH-VD) levels, semen parameters (ejaculate volume, total sperm count per ejaculate, sperm concentration, sperm progressive motility, and sperm morphology), and fertility hormones (follicle-stimulating hormone, luteinizing hormone, total testosterone, estradiol, and prolactin) were assessed.
Results: Mean 25-OH-VD was lower (18.4 (9.6) ng/ml) than the normal range. We found that testosterone was significantly lower in the group with 25-OH-VD ≤19 ng/dl when compared to the group with 25-OH-VD ≥20 ng/ml. There is a positive correlation between 25-OH-VD and testosterone levels. Although it was not statistically significant, there was a tendency for decreased sperm morphology.
Conclusion: Serum testosterone levels of men whose partners were diagnosed with IRPL decreased with lower 25-OH-VD levels. In addition to standard female factors, male factors should also be taken into consideration when evaluating the risk of IRPL.

Keywords: Idiopathic recurrent pregnancy loss, Male factors, Vitamin D, Testosterone, Spermiogram

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Introduction

Recurrent pregnancy loss (RPL) is defined as a female patient having two or more clinical pregnancy losses (miscarriages) before 20 weeks of gestation and affects 1–5% of reproductive-age women. Yet, clinicians recommend medical evaluation after just two miscarriages [1], which mainly focuses on female partners. Many factors may be involved in RPL, such as genetic, endocrinological, and anatomical abnormalities, autoimmune disorders, and infectious and systemic maternal diseases [2, 3]. Despite the extensive and expensive investigation of female partners, greater than 50% of cases are unexplained and defined as idiopathic recurrent pregnancy loss (IRPL) [4].

In recent years, an increasing number of researchers have investigated the effect of male factors on IRPL [5-7]. However, infertility clinics routinely evaluate paternal chromosomes. Recently, with the assisted reproductive technology procedures, the role of sperm factors has gained importance.

Semen parameters, including ejaculate volume, total sperm count per ejaculate, sperm concentration, progressive sperm motility, and sperm morphology provide useful insight into the quality of semen. However, the correct interpretation of these semen parameters for IRPL remains unclear [8–10]. Defective sperm DNA, with and without abnormal sperm parameters, is considered a reason of IRPL [9]. This led researchers to explore what may damage the sperm DNA. Regulation of male reproduction via modulation of the hypothalamus-pituitary-testes axis is important. As is known, hormones affect semen quality and sperm DNA [12]. Vitamin D (VD) levels may also affect spermatogenesis and serum androgen levels in men [13-16]. VD Receptor (VDR) which mediates the biological actions of VD, has been observed in reproductive tissues such as the ovary, uterus, prostate, testis, and human sperm [17, 18]. VD–metabolizing enzymes have been observed in the human testis, the ejaculatory tract, and mature sperm cells; therefore, VD plays an essential role in the maturation of sperm cells [19]. In one infertility study, vitamin D was positively associated with testosterone (T), and free androgen index but negatively associated with sex hormone-binding globulin (SHBG) [16]. However, there is a lack of data about the relationship between IRPL and VD levels in men as a male factor.

In this study, we aimed to investigate the association between 25- hydroxy-Vitamin D (25-OH-VD) serum levels and semen quality and reproduction hormones of men whose partners were diagnosed with IRPL.

Materials and methods

Patient selection

In this cross-sectional study, the data of 41 couples with a history of IRPL were collected. They had lost a minimum of two embryos during the first trimester and were referred to Infertility Clinic in the Medical School of Pamukkale University between February 2014 and February 2015. The female partners of the couples were examined fully and no cause was detected. These couples had not attempted assisted reproduction treatments at that time. On the other hand, the karyotypes of these couples were normal. No men had any history of radiotherapy, chemotherapy, chronic illness, or a family history of any diseases.

We noted age, smoking status, and previous varicocele operation history in all subjects. This protocol was approved by the local ethics committee and all patients were informed about the study.

Semen Analysis

Semen samples (one per subject) were collected by masturbation after 3-4 days of sexual abstinence in sterile plastic containers and left to liquefy at 37°C for 30 minutes. All semen analyses were performed by the same technician. Basic semen parameters (volume, count, concentration, and motility) were assessed according to the World Health Organization guidelines [20]. Sperm morphologies were assessed according to Kruger's criteria.

Hormonal analysis

Follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (T), estradiol (E_2), and prolactin (PRL) were assayed with an electrochemiluminescence immunoassay (ECLIA) (Elecsys Kit; Roche Diagnostics, Germany). Serum vitamin D levels were assessed by measuring serum 25-OH-VD levels using chemiluminescence immunoassay (Liaison Assay; Diasorin, Italy). 25-OH-VD levels were divided into two categories: 25-OH-VD ≤19 ng/ml (VD deficiency) and 25-OH-VD ≥20 ng/ml (normal) [21]. We had no subjects with 25-OH-VD ≥50 ng/ml. Seasonal variation of VD was excluded.

Statistical analysis

The Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis for the obtained values. The arithmetic mean of descriptive data, standard deviation, and percentage distributions were made. Mann-Whitney U test was used for non-parametric data and correlation analysis was performed. A *P*-value <0.05 was considered statistically significant.

Results

The mean age of the men who participated in the study was 31.7 (4.3) years. The mean duration of marriage and infertility were 5.34 (3.3) years, and 1.73 (0.8) years, respectively. The mean number of miscarriages was 2.7 (1.8), and the mean number of packages smoked per year was 2.6 (4.7). Only 13.9% of men had undergone varicocele operation.

The mean 25-OH-VD level was 18.4 (9.6) ng/ml. The mean 25-OH-VD levels of 27 patients (65.8%) were ≤19 ng/ml, while that of 14 patients (34.2%) were ≥20 ng/ml. The mean FSH, LH, T, E2 and PRL levels were 4.1 (2) mIU/mL, 4.5 (1.7) mIU/mL, 4 (1.7) ng/mL, 21.8 (8.5) pg/mL and 13 (8) ng/mL, respectively. The mean abstinence day, ejaculate volume, total sperm count per ejaculate, sperm concentration, percentage of progressive sperm motility and sperm morphology were 3.24 (0.4), 3.1 (1.5) ml, 291 (188) million, 102 (70) million/ml, 61% (16%) and 4% (4%), respectively.

Testosterone levels were lower in the IRPL group with 25-OH-VD ≤19 ng/ml when compared with the IRPL group with 25-OH-VD ≥20 ng/ml (P=0.008). There was no significant difference between these two groups in terms of other hormonal values (Table 1).

In our study, the semen parameters insignificantly changed with 25-OH-VD values. The ejaculate volume, total sperm count per ejaculate, progressive sperm motility, sperm morphology were numerically decreased in the low VD group (P>0.05).

Table 1: Demographical, hormonal and semen parameters per category of serum 25-hydroxy-Vitamin D level

	Serum 25-hydroxy-Vitamin D level		
	0-19 ng/ml (n=27)	20-50 ng/ml (n=14)	*P*-value
Duration of infertility (years)	1.8 (0.9)	1.5 (0.8)	0.190
Miscarriage	3 (2.1)	2.2 (0.4)	0.281
Smoking (packet x year)	3.25 (0.89)	5.03 (2.66)	0.136
FSH (mIU/mL)	4.1 (2.1)	4 (1.9)	0.941
LH (mIU/mL)	4.7 (1.5)	4.2 (2)	0.266
Testosterone (ng/mL)	3.1 (1.8)	4.3 (1.6)	0.008*
E_2 (pg/mL)	21.7 (10.2)	22.1 (4.5)	0.686
PRL (ng/mL)	12.9 (9.6)	13.1 (4)	0.571
Ejaculate volume (ml)	2.8 (1.3)	3.6 (1.7)	0.180
Total sperm count per ejaculate (million)	278.4 (187.2)	315.9 (194.6)	0.590
Sperm concentration (million/ml)	108 (79.7)	92.3 (49.2)	0.711
Progressive sperm motility (percent)	60.8 (16.3)	62.2 (18.6)	0.635
Sperm morphology (percent)	3.7 (2.1)	4.7 (2.1)	0.191

FSH: Follicle stimulating hormone, LH: luteinizing hormone, T: total testosterone, E_2: estradiol, PRL: prolactin. * P<0.05

Discussion

In the present study, we found that men whose partners were diagnosed with IRPL had decreased serum levels of 25-OH-VD. We also found that there was a significant relationship between serum 25-OH-VD and T levels. Because of the positive correlation between T and VD, serum T levels were lower in the VD deficient group. To the best of our knowledge, the role of VD on IRPL was not studied before. The literature about the role of VD on reproductive functions is preliminary, but VDR and VD metabolizing enzymes have been investigated in the reproductive tissues of males [21, 22]. Similarly, in an early study, VD was positively associated with T and free androgen index and inversely associated with SHBG [16]. Similar results were reported in some animal studies. VDR null mice had insufficient gonadal function with low sperm parameters and abnormal testis histology [23]. They were diagnosed with hypergonadotropic hypogonadism with high FSH and LH levels, and low T and E_2 levels due to reduced gonadal aromatase activity. Although the mating capacity was normal in VD-deficient male rats, they had decreased overall fertility [24].

The main reason for decreased T synthesis is lacking; however, 1,25-OH-VD treatment upregulates various genes for spermatogenesis in Sertoli cells [25]. The presence of VDR in human sperm displays a role in the capacitation and survival of sperm [26]. On the other hand, some researchers did not find a relationship between serum VD and T, E_2, LH, inhibin B [27]. Likewise, in another study, no significant differences were observed in terms of various hormonal parameters with different categories of 25-OH-VD levels [28]. The relationship of VD and fertility hormones is not reported in that study, probably because they chose participants from young healthy volunteers without any desire of procreating. With recent research, it became obvious that VD has a role in the reproductive proves, but related pathophysiological mechanisms require further larger investigations. We hypothesized that deficiency of 25-OH-VD is correlated with low testosterone levels in men with partners diagnosed with IRPL.

We also found that there was an insignificant association between 25-OH-VD levels and semen parameters. Ejaculate volume, total sperm count per ejaculate, progressive sperm motility, sperm morphology were lower in the VD deficient group when compared to the normal VD group with IRPL. There is scant data in the literature about the relationship between VD and semen parameters. Research showed that high levels of VD were related to lower total sperm count and normal morphology percentage, but low levels of VD were not related to sperm parameters [29]. They demonstrated that high VD might have caused toxicity in the male reproductive system. The findings of our study about sperm parameters in patients with normal VD levels are similar to those of the previous study. In our study, there were no patients with high 25-OH-VD levels (≥50 ng/ml) so we could only compare low and normal VD levels. Although statistical significance could not be shown, our data supported that low VD levels correlated negatively with most semen parameters. Blomberg et al. showed that low VD levels were correlated with reduced sperm motility, but high VD levels did not negatively affect sperm parameters [15]. Similarly, in a recent study, the association between low VD levels and semen parameters was asserted [30]. They found that VD deficiency was related to lower total progressive motile sperm count and lower total sperm count, but not related to sperm concentration, progressive motility, and morphology. Although we could not show the connection between VD and semen morphology in our study, poor semen quality, especially morphologic features, were the main characteristics of our IRPL group. In a recent study, the incidence of DNA fragmentation was increased in patients with poor sperm morphology compared with men with normal semen quality [31]. As expected, fertilization by spermatozoa with fragmented DNA results in a poor-quality embryo, decreased implantation rates, and higher pregnancy loss [32].

The relatively small study population limits the extrapolation of our study results. Further studies with larger populations are needed to validate our findings and explore the mechanism.

Conclusion

We found a negative association between 25-OH-VD levels and testosterone, which affects semen quality. Our results showed that poor sperm morphology and VD deficiency were related to pregnancy success. This study will hopefully make way for the development of new diagnostic methods in evaluating recurrent pregnancy losses without the female factor in the future.

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