Vitamin D: A new hormone in reproductive medicine

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<table>
<thead>
<tr>
<th>Search Key: vitamin d</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>METABOLIC SYNDROME, TYPE II DIABETES AND VITAMIN D IN POSTMENOPAUSAL WOMEN</td>
<td>Vartej IOANA (GR)</td>
</tr>
<tr>
<td>POLYCYSTIC OVARY SYNDROME AND SERUM VITAMIN D CONCENTRATION AND ITS RECEPTOR GENE POLYMORPHISMS</td>
<td>Milewicz ANDRZEJ (PL)</td>
</tr>
<tr>
<td>VITAMIN D DURING PREGNANCY</td>
<td>Perez-lopez FAUSTINO (ES)</td>
</tr>
<tr>
<td>THE ROLE OF VITAMIN D DEFICIENCY IN THE DEVELOPMENT OF GESTATIONAL DIABETES IN PREGNANT WOMEN WITH EXCESSIVE BODY WEIGHT</td>
<td>Pyrohova VIRA (UA)</td>
</tr>
<tr>
<td>THE PREVALENCE OF VITAMIN D DEFICIENCY IN WOMEN WITH INFERTILITY AND MISCARRIAGE.</td>
<td>Zazerskaya IRINA (RU)</td>
</tr>
<tr>
<td>DEPENDENCE OF THE SATURATION OF THE ORGANISM WITH VITAMIN D ON SERUM CONCENTRATION OF 25-(OH)-D DURING PREGNANCY.</td>
<td>Zazerskaya IRINA (RU)</td>
</tr>
<tr>
<td>DISTRIBUTION OF BONE MINERAL DENSITY BY DIFFERENT PARTS OF SKELETON IN PARTURIENTS WITH DIFFERENT LEVELS OF VITAMIN D.</td>
<td>Zazerskaya IRINA (RU)</td>
</tr>
<tr>
<td>CORRELATION BETWEEN BIOCHEMICAL PARAMETERS OF THE BONE METABOLISM AND VITAMIN D LEVEL DURING PREGNANCY.</td>
<td>Zazerskaya IRINA (RU)</td>
</tr>
<tr>
<td>VITAMIN D DEFICIENCY IN BREAST CANCER SURVIVORS</td>
<td>Tredici ZELINDA (IT)</td>
</tr>
</tbody>
</table>
• Vitamine D voor gezond sperma

30 JANUARI 2012 | NDN | Steeds duidelijker wordt dat voeding een grote invloed uitoefent op de vruchtbaarheid van man en vrouw. Uit recent onderzoek blijkt dat vitamine D van belang is voor de mannelijke vruchtbaarheid. Vitamine D verhoogt beweeglijkheid van het sperma.

Simple test doctors miss prior to fertility treatments

Vitamin D Has Been Shown to Dramatically Improve Fertility

February 16, 2012 | 107,070 views

Vitamin D: The fertility vitamin?
Introduction

- 1920 Rickets was prevented by a fat-soluble agent that was discovered in cod liver oil and was named Vitamine D.
- The steroid hormone is historically recognized for its relevance to bone formation.
- Recent years there is a shift in focus to non-skeletal benefits on the brain, colon, vascular smooth muscles, pancreas, placenta, prostate and reproductive system.
- Vitamin D Deficiency has been associated with increased risk of cancer, auto-immune diseases, CVD.
- Accumulating evidence from animal and human studies suggest that vitamin D is also involved in many functions of the reproductive system in both genders.
Introduction

- The predominant source of vitamin D is endogenous cutaneous synthesis.
- Dietary sources: < 20%
- Endogeneous synthesis of Vit D occurs after photolytic conversion of *dehydrocholesterol* located in the skin by ultra-violet B to *cholecalciferol or D3*.
- Nutritional forms of vit D consist of D3 which is found in fatty fish, eggs and calf liver, and *D2(ergocalciferol)* which is found in yeast and mushrooms.
- The circulating vit D is further metabolised by a set of liver enzymes, hepatic 25-hydroxylase, converts the prohormone to an intermediary metabolite 25-hydroxy vitamin D, whereas 1 alfa hydroxylase from the kidneys generates the *metabolically active form 1,25 di-hydroxy vitamin D*.
Introduction
Introduction

- The cellular effect of vitamin D is mediated through the intra-nuclear vitamin D receptor (VDR)
- VDR is expressed in variety of tissues other than the skeleton, including intestines, parathyroid glands, immune cells, pancreas, and more recently the hypothalamic-pituitary axis and reproductive tract.

Pandemic of vitamin D Deficiency
- The data of National Health and Nutrition Examination surveys in North America document a 4-fold increase in the prevalence of vit D deficiency.
  - Suboptimal dietary vit D intake
  - Increasing pollution
  - Reduced sun exposure
  - Increase use of sunscreen
  - Obesity
Vitamin D and Reproduction

- The presence of VDR in the ovary, uterus, placenta and testis suggest a regulatory role of vitamin D in reproductive physiology.

- The majority of experimental data are derived from diet-induced vitamin D deficient rodent models or mice. The available evidence makes a strong case for the importance of vitamin D for procreative success.

- The relevancy for reproductive health in humans is relatively recent.
Animal studies

- Inseminating female rats with sperm collected from diet-induced vitamin deficient rats resulted in 65% fewer sperm deposited in the genital tract.
  
  *Osmundsen et al J Steroid Biochem 1989*
  Multiple sites of action of vit D:stimulaion of the testis
  *Kwiecinsky et al J.Nutr 1989*
  Vit D is necessary for reproductive function of the male rat

- Diet-Induced vitamin D deficiency in female rats results in severely compromised fertility: 45-70% reduction in pregnancy, 67-100% reduction in viable pups.
  
  *Kwiecinski et al Am J. Physiol 1989*
  Vit D restores fertility of Vit D-deficient rats

- Exact mechanism is far from understood
Vitamin D and reproduction, relevance in humans

- In contrast with animal studies, literature describing the role of Vit D in the reproduction of humans is sparse.

- Serum levels of Vit D show a seasonal variation with high levels in summer and lower levels in winter.

- In Northern countries the conception rate is decreased in the dark winter, whereas a peak in conception during summer, leading to a maximum birth rate in spring. Ovulation rates and endometrial receptivity seem to be reduced in winter.  
  
_Rojansky et al  Fert and ster 2000_
Vitamin D and male reproduction, Human data

- Vitamin D metabolic enzymes are described in the human testis, the ejaculatory tract, mature spermatozoa and in the Leydig cells.  
  *Foresta et al Lancet 2010*

- CYP24A1 is a vitamin D-metabolizing enzyme. In a study comparing the expression of CYP24A1 in the ejaculated sperm from 77 subfertile and 50 healthy young men, the authors observed significantly reduced CYP24A1-expressing spermatozoa in the subfertile man compared with the healthy group. (p<0.001)  
  *Blomberg et al Andrology 2012*

- Man with VitD deficiency displayed a lower percentage of motile and morphologically normal sperm compared with Vit D sufficient subjects  
  *Blomberg et al Hum Reproduction 2011*
  
  *Vit D is positively associated with sperm motility and increase calcium in human sperm*
Vitamin D and male reproduction, Human data

A Cross-sectional study of 307 men, showed a trend for lower sperm parameters with higher vitamin D concentrations. This trend was not statistically significant.  

*Ramlau-Hansen et al Fert & Sterility 2011*  
Are serum levels of Vit D associated with semen quality? Results from a cross-sectional study in young healthy men

A recent European multi-center cross-sectional study of 3369 men (40-79j) showed a positive correlation between Vit D and testosterone concentration  

*Lee et al Eur J Endocrinology 2012*  
Association of hypogonadism with Vit D status: the European male Ageing study

A large cohort study of 2299 men showed a positive association between Vit D and testosterone  

*Nimptsch et al Clin Endocrinol 2012*  
Association between Vit D and testosterone levels in men
Vit D and Male reproduction

Human Data

Two small studies have attempted to provide evidence for a favourable effect of **vit D supplementation** on semen quality, testosterone levels and fertility outcomes.

**The first** randomised placebo-controlled study to evaluate the effect of vit D supplementation on testosterone concentrations in healthy overweight men undergoing an weight reduction programme. A significant increase in testosterone concentrations were observed in the Vit D supplemented group.

*Pilz et al Human Metab. Res 2011*

**Effect of vitamin D supplementation on testosterone level in men.**

**The second** was a randomised placebo-controlled trial in patients with prostatitis.

Vit D supplementation led to a significant reduction of IL-8 concentrations in semen which is compatible with improved quality and motility of sperm

*Tiwari et al Drugs 2009*

*Elocalcitol, a vit D analog for the treatment of benigne prostatitis and male infertility.*
Conclusion

• The data imply a role of Vitamin D in spermatogenesis, sperm maturation and endocrine function but additional studies are required to clearly define the importance of Vit D in male reproduction.
Vitamin D and female reproduction

VDR (Vitamin D receptor) are detected in the human endometrium, myometrium, ovarian, cervical and breast tissues. Vit D deficiency is hypothesised to contribute to a spectrum of gynaecological disorders of which PCO appears the most well studied.
Vitamin D and PCOS

- A small number of observational studies identify the inverse association of serum vit D and with insulin resistance, features of hyperandrogenism in women and circulating androgens in women with PCOS

  *Hahn et al Exp Clin Endocrinol Diabetes*
  
  *Low serum Vit D concentrations are associated with insulin resistance and obesity in women with PCO*

- Serum levels of Vit D are reported to predict ovarian response in women undergoing ovulation induction with clomiphene citrate. This was independent of the BMI. Low levels of vit D were found to be associated with lower rate of follicular development and pregnancy after ovarian stimulation with 50 mg clomid.

  *Ott et al Eur J Endocrinology 2012*
Vitamin D and PCOS

Supplementation Studies:

The first study was conducted in 1999
Thys-Jacobs et al described normalisation of menstrual cyclicity in 7 out of 9 oligoamenorrheic women with PCOS who underwent supplementation with Vit D over a period of 6 months

*Thys-Jacobs et al, Steroids 1999*

These results were confirmed in a later study:

A study of 60 subfertile women with PCOS were randomised in 3 groups, supplemented with vit D, metformin or both. Women with the combination demonstrated a higher number of dominant follicles.

*Rachidi et al Obst&Gyn 2009  Effects of Vit D on PCO, a pilot study*
Vit D and PCOS

Supplementation studies:

Others report that dietary supplementation with Vit D improves insulin sensitivity, circulating testosterone, and parameters of ovarian folliculogenesis and ovulation in PCOS:

- The effect of Vit D on insulin sensitivity calculated by glucose tolerance test was evaluated in 15 obese women with PCOS. An improvement of insulin secretion was observed.
  
  *Kotsa et al Fert & Ster 2009* Role of vit D treatment in glucose metabolism in PCOS.

- Another pilot study reported improvement of insulin resistance after vit D supplementation.
  
  *Selimoglu et al J.Endocrinol Invest 2010* The effect of vit D replacement therapy on insulin resistance and androgen levels in women with PCOS.
Vit D and PCOS

Supplementation studies:

- A 24 week study of 57 women with PCOS and mean BMI of 25.4 with a weekly regime of 20000U Vit D showed a significant decrease in fasting and stimulating glucose concentration. Approximately 50% of previously oligo- or amenorrheic women reported normalisation or improvement in menstrual cyclicity.

  Grundmann et al Reprod Biol Endocrinol 2011

Vit D Roles in reproductive health?
VIT D and PCOS

- Several data converge towards an beneficial effect of vit D in metabolic disturbances in women with PCOS. The studies are of small size and duration, lack of placebo control groups and widely accepted therapeutic cut off levels of Vit D. Larger placebo and BMI controlled trials with longer treatment periods are needed to clarify the favourable effects of Vit D in insulin resistant women with PCOS.

- The exact mechanism is not known
Vit D and In Vitro Fertilisation

Vitamin D and the reproductive succes in women undergoing IVF:

- In a prospective study of 84 women undergoing IVF Ozkan assessed the Vit D levels in ovarian follicular fluid and determined an association between vit D and cycle outcome. Follicular fluid levels were significantly higher in women achieving clinical pregnancy after fresh embryo transfer. (p=0.013)
  
  Oskan et al Fertil & Steril 2010
  Replete Vitamin D stores predict reproductive succes following IVF

- Others fail to confirm these association of Vit and IVF succesrate
  
  Anifandis et al Biol. Endocrinol 2010
  Prognostic value of follicular fluid VitD and glucose levels in the IVF-outcome.

- In a similar recent study of 82 infertile women, no correlation was found between serum or follicular fluid vitamin D concentrations and the IVF outcome.
  
  Predictive value of the level of vit D in follicular fluid on the outcome of IVF
Vitamin D and AMH

- AMH regulates the development of early pre-antral and antral follicles. It is one of the most reliable markers for ovarian reserve.
- No environmental factors have been shown to influence AMH, and factors such as day of the cycle, weightloss, smoking, pregnancy, contraception do not correlate with serum AMH levels.
- The promoter for the AMH gene contains a vitamin D response element and vit D upregulates AMH production in cultured prostate cells.
- Vitamin D is therefore a potential regulator of AMH concentration in blood.
Vitamin D and AMH

*Circulating Vitamin D correlates with serum AMH Levels in Late Reproductive-Aged women: Women’s Interagency HIV Study*
Zaher ey al Fertil Steril 2012

This study was nested within the WIHS study, the largest ongoing multicenter cohort study of HIV infection and related health conditions in US

**Multicenter cross-sectional prospective study**
388 premenopausal women where divided in 3 groups : age < 35, age 35-39, age >40.

**Main outcome measures**: correlation between Vit D and AMH after adjusting for HIV-Status, BMI,smoking,drug use, glucose and insuline levels, ..

**Results:**
For the youngest women AMH was negatively correlated with Vit D, whereas for the oldest women the relationship was reversed. The mean age at which the relationship was reversed was 35.

In women aged 45, Vit D was significantly correlated with serum AMH.
Vitamin D and AMH
Vitamin D and AMH

The level of serum anti-Müllerian hormone correlates with vitamin D status in men and women but not in boys.
Denis et al, Rev Endocrinol 2012 May

AIM: The objective of the study was to determine whether serum levels of AMH are related to 25-hydroxyvitamin D status.

SETTING: This was a correlative and intervention study.

PARTICIPANTS: Three cohorts of participants were analyzed; mature men (n = 113), premenopausal women (n = 33), and 5- to 6-yr-old boys (n = 74). Women were given a daily supplement of vit D or a placebo for 6 months and provided baseline and posttreatment blood samples.

MAIN OUTCOME MEASURES: Serum AMH and 25(OH)D were measured and analyzed for covariation.

RESULTS: Serum AMH positively correlated with 25(OH)D in men (r = 0.22, P = 0.02) but not boys. Both 25(OH)D and AMH levels exhibited seasonal variation in women, with an 18% decrease in AMH levels in winter compared with summer (P = 0.01). Vit D supplementation prevented seasonal AMH change.

CONCLUSION: Vitamin D may be a positive regulator of AMH production in adults. Vitamin D deficiency should be considered when serum AMH levels are obtained for diagnosis.
AMH and 25(OH)D levels are seasonal. Women were given daily doses of vitamin D3 (n = 16), D2 (n = 7), or a placebo (n = 10) over the autumn and winter months. The winter levels of 25(OH)D (blue) and AMH (yellow) are illustrated as the percentage of each woman's summer levels. The bar represent the mean + the sem. #, Significantly different from the summer values; #1, P = 0.001; #2, P = 0.01; #3, P = 0.003; #4, P = 0.03.
Vitamin D and AMH

Conclusion:
➢ The current studies suggest that vit D status effects a person’s AMH level.
➢ Vitamin D deficiency may need to be considered when AMH levels are low.
➢ Further studies should consider replacing vitD in women with vit D deficiency and assessing AMH bloodlevels.
Vitamin D and AMH

Vitamin D Deficiency and Ovarian Reserve Among Infertile Patients
This study is currently recruiting participants. (see Contacts and Locations)
Verified November 2013 by Universitair Ziekenhuis Brussel

Sponsor:
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Information provided by (Responsible Party):
Nikolaos P. Polyzos, Universitair Ziekenhuis Brussel

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Purpose
The role of vitamin D deficiency in female reproduction remains controversial. Early retrospective studies were inconsistent regarding the effect of serum 25-OH vitamin D levels on pregnancy rates in women undergoing in vitro fertilization (IVF), whereas two retrospective studies postulated that vitamin D deficiency may negatively affect pregnancy rates with an effect mediated through the endometrium.

Taking into account that knock-out experiments have shown that vitamin D receptor null mice not only experience uterine hypoplasia but also impaired folliculogenesis, it might be hypothesized that vitamin D deficiency may have a detrimental effect on female ovarian reserve. This may be further supported by previous reports demonstrating that serum 25-OH Vitamin D levels correlates with antimullerian hormone (AMH) levels in women of advanced reproductive age.

The aim of this study is to examine through a large set of prospectively recruited infertile women whether serum 25-OH-Vitamin D levels is related with the 2 most widely accepted biomarkers of ovarian reserve: serum AMH levels and antral follicle count (AFC).
Conclusion

- In the recent years emerging data suggested that vitamin D is not only critical for the maintenance of bone health but also imposes multisystem regulatory effects that modulates overall wellbeing and health.
- A growing body of literature suggests that Vit D may impact reproductive functions.
- Given its safety, accessibility and ease of administration Vit D supplementation could prove to be a cost effective therapy to improve public health.