

## Special Article - Vitamin D Deficiency: Clinical Cases &amp; Short Reports

# Faulty Perinatal Hormonal Imprinting Caused by Exogenous Vitamin D – Dangers and Problems

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**Abstract**

Hormonal imprinting takes place perinatally at the first encounter between the developing hormone receptor and its target hormone. The imprinting is absolutely needed and determines the binding capacity of the receptor for life. However, when the developmental window for imprinting is open, related molecules (other hormones of the hormone family, synthetic hormones, certain drugs, environmental pollutants [endocrine disruptors] etc) can bind to the receptor and faulty imprinting develops, which also has a life-long effect. The faulty hormonal imprinting is a functional teratogen. The transformed, active form of vitamin D (calcitriol) is a steroid hormone, the receptor of which belongs to the steroid receptor superfamily. Consequently, a single vitamin D treatment can execute faulty imprinting in the related receptors of the family. This causes life-long alterations in the hormone receptor's binding capacity, hormone synthesis of immune cells, ossification, brain neurotransmitter level, myocardial ouabain binding and sexual behavior, causing or helping the initiation of different diseases in adult age. The effect of hormonal imprinting is epigenetic and manifested also transgenerationally. The paper call attention that not only the problems caused by vitamin D deficiency could be considered, but the imprinting effect of the hormone excess. The change of vitamin-D name to hormone-D or, considering its many effects, multihormone-D is proposed, which could influence the mentality of the laity and doctors. In addition the thorough observation of human late effects is recommended.

**Keywords:** Perinatal exposure; Vitamin D; Hormones; Hormone receptors; Imprinting; Sexuality

**Introduction**

In the intrauterine life the fetus is regulated mainly by the endocrine system of the mother, as the maternal hormones can pass the placental barrier [1,2]. This situation is changed around birth, when the self endocrine system takes over the regulation. In this perinatal period the developing hormone receptors and the self hormones meet each other and hormonal imprinting develops, which life-long influences the receptor-hormone connections [3-5]. Imprinting is needed for the normal regulation. However, in that time, when the developmental window for imprinting is open, molecules similar to the target hormones (members of the same hormone family, hormone analogues, drugs, environmental pollutants, as endocrine disruptors) as well as the overweight of the physiological hormones also can influence the further development of the receptors, and faulty imprinting develops [3-5]. The alteration of the affinity of the receptors are infrequent, the change of binding capacity is regular. Many diseases can be deduced to perinatal harms [6-9] and faulty hormonal imprinting has a leading role in it. The faulty hormonal imprinting is a functional teratogen [10], which causes many functional alterations and manifestation of diseases in adult age [11].

Vitamins are such molecules which are not produced by the organism however, they are vital for life. Vitamin D is synthesized by the cells of the skin under the effect of the sun (UV-light) however, it

is also taken up in foods. The activated form of vitamin D (calcitriol) is not a vitamin, but a hormone. While other (water-soluble) vitamins are co-enzyme precursors, calcitriol is bound by vitamin D receptors, which are members of the steroid receptor superfamily. When exogenous vitamin D gets into the organism perinatally, its active form (converted by the liver and kidney) [12-14] can be recognized and bound also by receptors of steroid hormones and can execute faulty hormonal imprinting on them, causing life-long consequences. A single encounter between vitamin D and its false target receptors is enough for developing the faulty hormonal imprinting.

**The effects of perinatal vitamin D imprinting in animal experiments**

In contrast to the flood of experiments and observations which are involved in the harmful effect of vitamin D deficiency, the studies on the deleterious effect of single or prolonged vitamin D treatment perinatally are practically absent in men, and scanty in animal experiments. However, the observations call attention to the possible harmful effects of these treatments.

Vitamin D was registered for a long time as an ossification influencing vitamin and only in the last time come to the front its other- equally important- effects. A neonatally given single dose (0.05 mg) cholecalciferol- vitamin D<sub>3</sub>- significantly reduced bone mineral density (BMD) measured at 3 months old rats in both sexes and bone mineral content (BMC) in males [15]. However, in contrast

to this harmful effect, vitamin D treatment in adult age of rats which were neonatally dexamethasone treated and have reduced BMD, were compensated by vitamin D treatment at adult age [16].

The neonatal vitamin D imprinting was ineffective to the hormone production of immune cells in contrast to the effect of the other vitamin-hormone, vitamin A [17-19]. However, there was a transgenerational effect, when in the first progeny generation of neonatally vitamin D treated mothers the histamine and triiodothyronine contents of immune cells decreased to one-third [18,20].

Single neonatal imprinting with 0.05 mg cholecalciferol significantly elevated the dopamine level of 3 months old animal's brainstem and homovanillic acid level (dopaminergic system) of striatum and hypothalamus [21] in contrast to vitamin A imprinting, which influenced the serotonergic system. The brain effect of neonatal imprinting was transgenerational and manifested also in the F1 generation, where elevation of neurotransmitter levels was also found [22] and biogenic amine levels was strongly disturbed, brain area dependently.

Single neonatal low-dose (25 microgram) imprinting with vitamin D3 significantly decreased the thymic glucocorticoid receptor density of 6-week old male rats, meanwhile it was ineffective in females [23].

Perinatal imprinting with vitamin D3 enhanced the ouabain binding capacity of myocardial Na,K-dependent ATP-ase, when adult [24].

Vitamin D imprinting with a small dose completely inhibited the ejaculation of male adults without apparent influence on sexual desire. Imprinting with a large dose reduced both ejaculation and desire and the sexuality of females was also depressed [25], similar to synthetic steroid hormone analogues and benzpyrene [26].

Prostate has calcitriol receptors [27]. Pregnant rats were treated with low doses of calcitriol on alternate days up to labour [28] and the weight of prostate was measured. At the time of puberty the prostate of the treated animal's progenies was 35% higher, than control and 68% higher in adults. A high mortality rate (71%), caused by sudden death was observed at puberty in the treated rats.

## Conclusion

As it was written above, faulty hormonal imprinting develops, when a molecule similar to the receptor's target hormone binds to the receptor in a critical developmental stage, perinatally. These molecules are first of all members of the same hormone family, synthetic hormones, environmental pollutants or drugs with hormone-like structure. It was mentioned that vitamin D is not a vitamin, but a molecule synthesized by the skin (under the effect of sunshine), or which are present in some foods. This molecule is transformed in the liver and kidney to the hormone, calcitriol (25-hydroxyvitamin D) and this is recognized by the vitamin D receptor (VDR), which is a member of the Steroid Receptor Superfamily (SRS). As other members of this family are the sexual steroid (testosterone and estrogen) receptors, the corticoid hormone receptors, the thyroid hormone (T3 and T4) receptors, the vitamin A (which is also a hormone) receptors, perinatal vitamin D treatment is able to provoke faulty imprinting on them. The effect of a single encounter between these receptors and

the active form of vitamin D develops the life long effect in animal experiments. As it is shown by the results listed above this is not a hypothesis, but a fact. As the members of SRS are present in many organs and cells everywhere in the organism, the faulty imprinting by vitamin D can cause a lot of alterations. In addition, vitamin D receptors are present in 36 cell types [29], influencing 291 genes [30], and faulty imprinting (by vitamin D excess) can be executed on them. However, while vitamin D insufficiency or deficiency causes diseases or can be fatal, hormonal imprinting caused by hormone excess perinatally results in milder alterations, which become dangerous when have a channel in a certain period of life, e.g. in puberty or climax etc. The best example of this late effect was the Diethylstilbestrol (DES) catastrophe, when DES treated (for protecting endangered pregnancies) mother's daughters besieged hospitals upon thousands, because of vaginal cancers or precancerosis, almost two decades after the treatment of mothers [31-33]. While the effect of vitamin D deficiency is immediate, the effect of imprinting by excess is prolonged and causes problems decades later. This can explain, why the long-lasting effect of perinatal vitamin D deficiency and supplementation has a plethora of experimental papers and human observations, while hardly can find informations on the instant and late effects of single perinatal treatments (hormonal imprinting) or permanent perinatal supplementation.

Although the spectrum of perinatal vitamin D imprinter effect was broad on the basis of the animal experiments, the faulty imprinting of sexual steroids seems to be one of the most important. A single low dose vitamin D treatment (perinatally) inhibited ejaculation in adult males and depressed sexual activity of females, as well as long treatment during gestation enormously increased the weight of prostate. High dose completely abolished sexual desire in males and females alike. In other experiments environmental pollutants had similar effects [26,34]. These effects are understandable, knowing that vitamin D influences steroidogenesis and VDR is present in the ovary, in the pituitary gland, in human sperm and epididymis [35]. However, while endocrine disruptors do not touch equally the whole population, in the case of the recommended enforced vitamin D supplementation [36] the faulty imprinting can not be avoided [37]. It must meditate on this problem as there are many changes in the sexuality of today's men (earlier sexual maturation, more sexual aggressivity and aberrations, homosexuality etc), and they can be attributed to the change of chemical environment, including perhaps the perinatal vitamin D treatments. Considering these facts, difficult to agree with such opinions that, "it is generally accepted that supplementation/treatment is not harmful and may have some significant result and long-term benefits" [38], as thorough investigations on the late effects are not done, and the proposal of Drugs and Therapeutics Committee of the Pediatric Endocrine Society for studying the calcitriol levels of perinatally vitamin D supplemented children is not extended to the adult age to clear other possible negative effects [39].

It is unquestionable, that perinatal exogenous vitamin D exposition influences the binding capacity of related steroid receptors however, there is not experiments on the effect of this treatment to the receptors of its own. Perinatal hormone excess makes faulty imprinting also in the self-receptor in general, and this can be measured by adult's receptor binding capacity [5]. However, there is not such experiments in case of vitamin D. Theoretically imprinting is

taking place and this has to influence the later reactivity of VDRs to the vitamin-hormone, which can be manifested in the change of vitamin D requirements at adult age, as well as prostate cancer development [40,41]. It is also important to know that in men, perinatal vitamin D rarely imprints alone, as other faulty imprinters are often present and acts together [41]. This can change the effect and direction of imprinting.

Vitamin D is an important modulator of brain development [42,43], as vitamin D receptors are present and working in the brain [44,45]. During critical periods of development there is a possibility of reprogramming the brain by vitamin D [44]. This could lead to brain tumors. Imprinting by vitamin D influenced the brain biogenic amine levels and this effect is transmitted to the progeny generation. Its interaction with dopamine synthesis could have a role in the development of autism and schizophrenia [46-49] similarly, as it could be dependent on the imprinting by an other hormone, oxytocin [50-52]

Hormonal imprinting is an epigenetic process. This means that without changing the DNA sequences, the regulation of genes are influenced for life. This happens first of all by the change of methylation patterns, however histones and RNA are also altered and regulates the expression of genes. This changes are responsible for the altered reaction of cells of imprinted animals. In case of faulty imprinting the methylation pattern is abnormal and depending on it, the hormone production (and the influenced function) is touched. However, the epigenetic character of hormonal imprinting also means that the effect is manifested not only in the treated animal (person) but also in the progenies [38,39,50]. This seems to be supported by many cases of perinatal imprinting in animal experiments, e.g. effect of single neonatal treatment with an endocrine disrupting chemical [53], benzpyrene [26,34] and there are a lot of human observations to justify them [54-56]. The consequences of epigenetic alterations (epimutations) are manifested in metabolic, reproductive and neurological modifications as well, as in the psychical phenotype (behavior) in the progeny generations, while promote the genetic instability [57-59]. For this, sometimes not more, than the change of the type of nutrition in critical developmental periods seems to be needed [60-64].

As it was shown, in the case of vitamin D, the transgenerational effect was justified in two cases: when hormone synthesis changed after imprinting and when brain neurotransmitter level of the perinatally vitamin D imprinted mother's progenies showed changes. If it is true in human relations, further generations will be influenced by the present day vitamin D supplementation campaigns [15] and the vitamin D treatments of further generations will be settled on the imprinting-influenced receptors of preceding generations [65].

Although the perinatal period is the most sensitive for hormonal imprinting, there are other critical phases. For example, in adolescent age vitamin D imprinting can be executed on liver glucocorticoid receptors, which results in a life-long elevation of the receptor density [66]. At the same time, treatment of adolescent animals significantly decreased thymic glucocorticoid receptor density, but only in males [23]. There are such organs or cells, which are sensitive to hormonal imprinting during the whole life: e.g. developing haemopoietic cells can be permanently imprinted [4,5].

The regulation of ossification was believed the primary (exclusive?) role of vitamin D for a long time. The importance of this role does not decreased in the present days, only other, sometimes equal important functions have been recognized. The faulty perinatal vitamin D imprinting significantly influences the ossification as it was demonstrated by the listed experiments [15,16]. In addition, these experiments called attention to the gender dependence of vitamin D imprinting [16] which were also manifested in other cases [17,23]. For the dependence, the presence of different sexual-steroid milieu could be responsible, i.e. the co-operation of different sexual hormones and vitamin D in the provocation of faulty hormonal imprinting.

A fundamental problem is—considering the faulty imprinting effect - in the case of vitamin D, its name. Vitamin is a quite another category than hormone. In the mentality of laymen vitamin is a beneficial material, which is needed for health in contrast to hormones which are effective serious regulators, requesting the consideration of doctors. This opinion is supported by TV advertisements, which propagate vitamin D and multivitamins as well, as calcium preparations, containing also vitamin D which can be purchased without prescription. Doctors are knowing that vitamins can be harmful (dependent on type and dose), however, this opinion is weakened by the vitamin name. If vitamin D would be called hormone-D, or multihormone-D (a similar situation is in the case of vitamin A), and recognized as a hormone, advertisements would not be possible and less prescription would be given. At present, vitamin D is a harmless miracle-drug, recommended to almost all of the diseases for adults and infants, for prevention and treatment, and considering or disregarding its imprinting effect, this seems to be dangerous, because of its steroid hormone character.

Perinatal vitamin D deficiency is hazardous, causing, initiating or helping the acute and late manifestation of many diseases. This does not allow to neglect the perinatal supplementation, however the optimal mode of this is not known [44,67-69]. Faulty vitamin D imprinting is also dangerous, causing changes in the methylation of epigenome [70] and by this, late disturbances in steroid (and sometimes other) hormone effects and by the possible help of the manifestation of endocrine and other diseases and also causing problems in sexuality. In addition, faulty imprinting threatens with epigenetic inheritance and consequently evolutionary alterations [71]. However, the comparison between the perinatal flood of papers recommending perinatal vitamin D supplementations and the cautious handling of the imprinting problem is unfair, as the effect of deficiency is causing acute problems (diseases), while hormonal imprinting provokes late effects (if the connection between the imprinting and its late result in men is recognized at all). What is to be done? This is a difficult question and the answer is uncertain. It is recommended to rename the vitamin to hormone and call attention to its possible late dangers. It must be further studying the pathological effects of faulty perinatal imprinting as well, as the optimal perinatal time and optimal dose of hormone-D treatments. And in the possession of knowledge, it must tolerate the responsibility for the late problems caused by the treatments or non-treatments.

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