

# Functions - Statement on the effects of excess Vitamin A on maternal health

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## Functions

17            Retinol performs many important physiological functions in animals. It is involved with the synthesis of collagen and elastin fibres by fibroblasts, as well

as in cell division and differentiation, and the functioning of skin and mucous membranes. Vitamin A influences bone development by regulating the activities of osteoblasts and osteoclasts. It decreases the secretion of thyroxine from the thyroid gland by suppressing production of thyrotropin by the pituitary gland. Vitamin A also stimulates the immune system and hence improves resistance to infections. (Rutkowski and Grzegorzczuk, 2012)

18 Vitamin A is an antioxidant: the conjugated C = C bonds in the side chain are oxidised by reactive oxygen species (ROS) and free radicals and thus protect those bonds in the polyunsaturated fatty acids in cell membrane lipids. This also protects against uncontrolled oxidation of the glycosyl residues of proteins in cell membranes, which can play a role in neoplastic transformation (promotion). The antioxidative function also stabilises thiol groups (-SH) of membrane proteins and suppresses oxidatively stimulated expression of the c-myc oncogene. Epithelial cells in particular are protected against oxidative damage by vitamin A, including tissues of the nasal and throat cavity, oesophagus, stomach, intestines, respiratory tract, bladder, and prostate. (Rutkowski and Grzegorzczuk, 2012)

19 Retinol is oxidised to retinal (vitamin A aldehyde or retinaldehyde) which, as its 11-cis isomer, functions in the retina (in the pigment, rhodopsin, in the rods and the pigments of the cones) as an essential component in the process of visual signal transduction (EVM, 2002).

20 Retinal is further oxidised to RA and then undergoes further side-chain isomerisation and oxidation into a range of different products. RA has pleiotropic (multiple phenotypic) effects in development and is well documented in the literature as a teratogen (Collins and Mao, 1999).

21 Retinoids are used clinically to treat a range of disorders including skin lesions and cancers. A range of synthetic analogues, with enhanced receptor specificities and pharmacokinetic profiles, has been developed in order to maximise the benefits of treatment whilst ameliorating their toxicity. Barnard et al. (2009) reviewed the design and structure of a wide range of synthetic retinoids with modified beta ionone heads, isoprenoid chains and hydrophilic end groups to explore this pharmacological space.

## **Mechanism of action**

22 The majority of the effects of ingested vitamin A are thought to be mediated by the action of RA. Since RA is produced endogenously and binds to

specific nuclear receptor proteins that then bind to DNA and regulate the expression of various genes, it is classified as a hormone. It is a ligand for specific nuclear receptors, the most studied of which are RA receptor (RAR) and retinoid X receptor (RXR), that regulate the transcription of numerous target genes, as homo- or hetero-dimers. More than 500 genes are known to be regulated by RA, many of which control embryonic development. RA signalling is turned off by ligand degradation by P450 (CYP) enzymes, such as CYP26A1.

23            Das et al. (2013) and Huang et al. (2014) detail the molecular biology and functions of the retinoid receptors. Studies have shown that RA plays a crucial role during skeletal development and in ensuring the suppression of left-right asymmetries during developmental pattern formation in embryos. RA is not produced by all cells of the body at all stages of development but is produced in a unique spatiotemporal pattern which orchestrates development. Further molecular detail is provided in the [discussion paper on the effects of excess Vitamin A on maternal health](#).

24            In preparation for implantation of the fertilised ovum, progesterone released from the corpus luteum causes the cells of the superficial layer of the endometrium to enlarge and compact. These cells are known as decidual cells because they are shed after birth and the process is decidual transformation (Bowman and Rand, 1982). Ozaki et al. (2017) showed that decidual transformation of human endometrial stromal cells (HESCs) resulted in reprogramming of the RA signalling and metabolic pathways. The authors concluded that the data showed that decidualizing HESCs silence RA signalling by downregulating key cytoplasmic binding proteins and by increasing retinoid metabolism. However, excessive RA exposure is detrimental by triggering a response in decidual cells that can lead to pregnancy failure. Further molecular detail is provided in the [discussion paper on the effects of excess Vitamin A on maternal health](#).

25            Both deficiency and excess of RA causes the ectopic induction and the down regulation of many genes as a prelude to changing the morphology of the embryo. For example, excess RA causes the chick limb bud to develop six digits instead of the normal three (Tamura et al., 1997). Conversely, quail embryos deficient in RA have down-regulated genes, but also express ectopically induced genes, probably by the downregulation of a repressor, also leading to limb malformations (Stratford et al. 1999).

26            The hindbrain of embryos is also profoundly affected by vitamin A. RA administration to mouse embryos induced the hindbrain Hox genes in an altered

expression pattern, which resulted in an altered morphology, with the seven structures in this tissue known as rhabdomeres developing in the wrong order, leading to malfunction of the whole brain region. Marshall et al. (1992).

27 Carazo et al. (2021) reviewed the forms, sources, detection, kinetics, function, deficiency, therapeutic use and toxicity of vitamin A. They concluded that “Given the importance of vitamin A in multiple crucial physiological processes, its deficiency can pose a serious health challenge, even leading to death in the most serious cases. At the same time, it can lead to serious health issues in high-dose situations.”