VITAMIN A AND GESTATIONAL DIABETES

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ABSTRACT

Diabetes *mellitus* (DM), a pathology with chronic evolution, has now acquired a connotation of global epidemic. Gestational diabetes, a condition associated with insulin resistance and decreased β-cells function is also characterized by a high incidence in different populations and ethnic groups. Recently strong evidence has been found for involvement of retinol levels of pregnant women with DM due to the pathology's evolution. This condition makes these patients prone to having a marginal biochemical profile or a vitamin A deficiency when compared to healthy pregnant women. Therefore, with an awareness of the physiological role of vitamin A and consequences of diabetes during pregnancy, this review intends to clarify the impact of DM on retinol levels of these pregnant women and the consequences that vitamin A deficiency may cause to these women and their infants.

Key words: Vitamin A. Vitamin A Deficiency. Vitamin A deficiency. Diabetes mellitus.

INTRODUCTION

Diabetes mellitus (DM), due to its growing incidence, is today a global epidemic. DM is a chronic and evolutive pathological process involved in metabolic disorders of various nutrients and is characterized by defects of insulin secretion, in its action or in both, with resulting hyperglycemia.[1] This alteration in glycemia during gestation might have consequences on maternal, fetal and perinatal health, causing serious complications.[2,3]

Currently, there is evidence of a strong association between DM and serum retinol levels in pregnant women.[4] The presence of this pathology during gestational period makes these women prone to presenting a marginal biochemical state or vitamin A deficiency.[4] This condition, in addition to potentializing complications caused by diabetes evolution in pregnant women, will render their children more vulnerable to the development of one of the most prevalent and important global deficiencies, that of Vitamin A,[5,6] when compared to those with healthy gestation.

Due to the impairment in maternal vitamin A transference, gestational diabetes is characterized as an aggravating factor not only in the incidence of xerophthalmia, but also on the mortality rates for pre-school children, since it will impair the formation of vitamin A reserves in the newborn.[6-8] Despite this condition, there is little guiding in literature for the diabetes mellitus' effect on vitamin A levels in these patients, the main focus still being on the influence of dietary composition in this pathology's control.

Gestational diabetes

Diabetes mellitus is not one single disease, but a heterogeneous group of metabolic disorders presenting hyperglycemia as a common feature. This hyperglycemia is the result of defects in the insulin's action, in its secretion or in both, and its long-term consequences originate from micro and macrovascular alterations that lead to dysfunction, damage, or failure in several organs. Chronic complications include nephropathy, neuropathy, amputations, Charcot arthropathy and autonomic dysfunction manifestations, including sexual dysfunction.[9,10]

Current classification of diabetes mellitus is based on its etiology and includes four clinical classes: type 1 (DM1), type 2 (DM2), gestational diabetes (GD) and other less common types with varied clinical presentation, depending on the base alteration.[10]

GD is considered to be any decrease in tolerance to glucose, of variable magnitude, diagnosed for the first time during gestation, persisting or not after delivery.[10,11] Similarly to DM2, GD is associated both with resistance to insulin and decrease of β-cells function, which are capable of satisfying the growing organic needs of insulin.[4]

According to the Brazilian Multicenter Study on Gestational Diabetes promoted by the Brazilian Ministry of Health in the 1990s, GD's prevalence in women over 20 years old seen in the Unified Health System (SUS) is 7.6%.[12] In Brasilia, with data collected in the period of 2005-2006, GD's prevalence was 6.6%.[13] However, in the United States, with 2002 data, it was estimated that 8% of the more than 4 million gestations were

associated to diabetes, and, among these, 88% had GD and 12% presented diabetes originating prior to gestation.[3]

Gestation is a condition that naturally predisposes to insulin resistance (IR) and its purpose is providing nutrients preferentially for the fetus. This IR may be the result of a combination of maternal adiposity, calories ingestion and the effects of insulin sensitivity reduction caused by placental hormones, such as HPL, human placental lactogen, which presents itself in growing levels from the second trimester and is responsible for IR.[3,11] During gestation, cortisol, estrogen, progesterone and prolactine are also increased, diminishing the insulin sensitivity.[3] Due to IR, gestation is characterized by the elevated level of circulating insulin, once the pancreas, in non-diabetic women, compensates for the increased peripheral demand, maintaining normal levels of glycemia.[11]

Gestational diabetes is associated with high risk both for fetus and mother, due to the increase in prevalence of congenital anomalies and spontaneous abortions and to the risk of presence of microsomia, hypoglycemia, hyperbilirubinemia, hypocalcemia, polycythemia and respiratory distress syndrome in the fetus.[3]

DM treatment during gestation aims at a good glycemic control; when this control cannot be obtained through diet, associated or not with physical exercises, an indication for insulin therapy is established.[2]

Vitamin A: metabolism and functions

Vitamin A (VA) is a generic term for a group of composites with similar biologic activity, such as retinol, retinal, and retinoic acid. The term 'retinoids,' on its turn, comprises both these natural forms of VA and many synthetic analogues to retinol.[14] This vitamin acts in two levels in the organism: the first, in the retina, participating in the visual cycle; and the second, in all the body tissues where it systematically maintains growth and integrity of cells.[15] Thus, it is fundamental, for the visual system's normal functioning; growth, differentiation and maintenance of cell epithelial integrity, immune function and reproduction.[15] Dietary needs of VA are usually contemplated in the form of preformed vitamin A and provitamin A carotenoids, both presenting absorption in the level of intestinal mucosa.[15,16]

Due to being a liposoluble vitamin, it depends, for its optimum metabolism, on all the lipid components involved in micelle formation, as well as that of pancreatic and biliary functions.[17] Retinol absorbed may be released directly in extra-hepatic tissues or captured by the liver, where it might be stored in the stellate cells or returned to the blood flow to supply the organism's needs.[14,18]

Retinol's plasma transportation is possible due to its association with a protein with specific transportation function, RBP, retinol-binding protein. In addition to this function, RBP is useful to solubilize liposoluble vitamin in the serum, to protect it against oxidative destruction and maintain it under a constant concentration in the circulation.[19]

RBP is synthesized in a higher extension by hepatic parenchymal cells, initially as uncoupled RBP (apo-RBP) and, when secreted in the circulation, transporting retinol in a molar fraction of 1:1,[20,21] holo-RBP binds transthyretin (TTR) to form the ternary complex retinol-RBP-TTR with a higher molecular weight ($\approx$85 kD). TTR prevents extensive RBP loss through glomerular filtration, enabling retinol provision to target tissues according to their metabolic need.[20,21] In these tissues retinol uptake may occur by simple diffusion through the lipid bilayer[16] or RBP-specific cell surface receptors that mediate retinol transportation to the cells' interior.[19] Many tissues express these receptors, among them the placenta, testicles, choroid plexus and macrophages,[19] besides mammary gland.[22]

During gestation and lactation period, diverse physiological mechanisms are involved with the adequate provision of maternal VA to the infant. The responsible mechanisms for transferring ingested VA to the mammary gland and its consequent secretion in the milk are not fully understood in humans. However, it is known that in animal models, VA is transferred to milk in two ways: retinol-RBP complex and chylomicrons.[23,24]

Retinol-RBP complex is responsible for more than 95% of the VA present in the circulation at fasting states.[25] Under this condition, and also in face of basal VA ingestion, it is suggested that less than 70% of retinol found in milk is transferred to mammary gland through RBP and around 30% through chylomicrons;[23,26] for such hepatic reserves must be severely depleted for limiting the availability of the retinol to be secreted through holo-RBP.[24] Chylomicrons' contribution, on its turn, will be increased under conditions of increasing VA ingestion or supplementation, this fact being a consequence of the intensification of lipoprotein lipase in mammary gland during delivery and lactation.[23,27]

Two mechanisms are also responsible for VA transference from mother to infant: placenta during gestation and mammary gland (breast milk) during lactation. However, the transference through mammary gland provides 60 times more VA in the first six months of breastfeeding when compared to the placenta during the whole gestation.[5]

Due to the visible efficiency of its transference mechanism, breast milk is highly beneficial for the infant, mainly when it is known that its hepatic VA reserves are very limited at birth, due both to a tendency to seric retinol levels decrease in pregnant women, mainly in the last trimester of gestation, and to the existence of a placental selective barrier which prevents the passage of this vitamin to the fetus in order to avoid possible teratogenic effects.[6,28]

Thus, in ideal breastfeeding conditions, breast milk is considered the most important source of VA to multiply the infant's hepatic reserves and the great protective factor against Vitamin A deficiency (VAD) until two years of age, the peak of vulnerability.[29] However, certain maternal factors may influence retinol concentrations in breast milk, among them the lactation stage;[30] breastfeeding process;[31] gestational age;[32]; parity[33]; VA in maternal diet;[34] zinc's nutritional state;[22] and pathologies as diabetes mellitus.[35-39]

Vitamin A: RBP and diabetes mellitus

Individuals with diabetes mellitus have been considered a group in risk of presenting marginal nutritional state or deficient in many related micronutrients and composites, such as vitamins A, E, C and carotenoids.[38-40] Accordingly, women with gestational diabetes have also been suggested as a group in risk of presenting reduced VA levels.[4]

In accordance with Basu et al., (1997)[38] among interfering factors in seric vitamin A concentration, the presence of DM does

not seem to affect ingestion neither intestinal absorption. This way, the deficient state observed must be related to the vitamin's impaired transportation. The impairment of its metabolic availability is observed both in decompensated diabetes patients and streptozotocin (STZ) rats-diabetes induced[35,36,38] and Bio-Breed (BB) rats,[37] evidenced through decreased seric retinol levels and seric and hepatic RBP.

Studies suggest that the presence of hyperglycemia is a causative factor for the imbalance in retinol levels and RBP, since VA provision from hepatic stocks was normalized after insulin treatment and remained reduced after supplementation of vitamin A, alone or combined with zinc.[36,37] Despite zinc's nutritional state being related to protein carriers' synthesis, its supplementation (120μg/g diet during four weeks) was inefficient to improve VA's seric concentration when diabetes is present.[36]

Compensated diabetic patients, not dependent on exogenous insulin, remain with their vitamin A status unchanged,[38] since they may present high levels of endogenous plasma insulin due to their reduced insulin sensitivity or IR. The correlation between serum levels of RBP secreted from adipocytes (RBP4) and plasma insulin suggests the existence of a limit in which plasma insulin allows the increase of RBP expression.[41] Therefore, the result of these two studies corroborates that insulin secretion is determinant for vitamin A's metabolism in DM. In addition, Chertow et al. (1987)[42] have established another relation between VA and insulin in establishing that retinoids are required for the adequate insulin secretion.

Although several studies currently focus on the relation between RBP and diabetes,[35-46] some results are still conflicting, and this is due mainly to the different methodologies adopted. For this reason, the mechanism responsible for alterations in vitamin A levels and the presence of diabetes has not been entirely elucidated.

Vitamin A: deficiency and diabetes mellitus

Among nutritional deficiencies of greatest epidemiological importance, vitamin A deficiency (VAD) still today assumes severe proportions in the public health context as a whole. According to the World Health Organization, nocturnal blindness affects 5.2 million children in pre-school age and 9.8 million pregnant women globally. Low serum retinol concentrations (<0.70 μmol/l) affect around 190 million children in pre-school age and 19.1 million pregnant women.[47] In our country, according to data of the National Research on Children and Women Demography and Health (2006), 17.4% of the children and 12.3% of the women presented inadequate VA levels. Among children, the most alarming rates are those related to Southwest (21.6%) and Northeast (19%).[48]

It is known that a permanent VAD state will impair physiological functions, both in children and in adults, even if clinical signs of deficiency are not evident.[49] Considering that the presence of gestational diabetes aggravates the tendency to VAD development in these women, the provision of proper quantities of this vitamin for their infants will be damaged, making them vulnerable to presenting limited stock of vitamin A in the body.[4,6,34]

This way, this nutritional disorder may cause an increase in mortality, morbidity and blindness in these children. It is known then that pre-school children with deficient vitamin A reserves

in the body present a higher risk of death by diarrhea, respiratory infections, and chicken pox than children with adequate vitamin A state, since it has a protective role against these complications.[6-8]

VAD is the main cause for permanent blindness followed by death among children in developing countries, contributing also to a significant increase in children morbidity and mortality rates associated to infectious processes.[50] In VAD, the integrity of epithelial barriers and immune system are involved before visual function alterations,[49] possibly impairing the immune response, leading to a higher prevalence and severity in infections, involving the healing process, which is so important for the diabetes mellitus patient.[38]

Studies report that in the case of decompensated diabetes, VAD may not be improved with supplementation. In this case, due to metabolic alterations, the practice of supplementing vitamin A may increase its concentration in the liver, leading to a hepatic toxicity.[35,36] Moreover, VAD predisposes pregnant women to spontaneous abortion and higher severity in gestational intercurrences, besides being associated with infections, anemia, and the development of hypertensive pregnancy syndromes.[51]

Knowing VA's relevant physiological roles and the factors influencing their concentrations, the need of monitoring this vitamin during gestation becomes clear, mainly if it is accompanied by diabetes mellitus, in order to prevent the emergence of other pathological complications for mother and infant.

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