INTRODUCTION

Pregnancy is a state of metabolic challenge, and as such even a normal, healthy pregnancy is a state of oxidative stress compared with non-pregnancy, and is a challenge to be met by the mother and her developing baby. Due to its high metabolic rate and level of mitochondrial activity, the placenta is a key source of this oxidative stress ***(Miller et al., 2012).***

Oxidative stress implies that the production of pro-oxidant free radical species exceeds the capacity of cells within an organ to neutralize or scavenge them. The capacity of placental antioxidant defenses to mitigate the effects of highly reactive and potentially damaging radicals is critical for healthy placental function and optimal growth and development of the fetus ***(Miller et al., 2012).***

Oxygen free radicals have been implicated in the etiology of premature delivery, fetal growth restriction, eclampsia, maternal infections and maternal malnutrition. Risk may, however, depend on the mother's antioxidant status which potentially protects the maternal–fetal unit, thus increasing intrauterine growth and infant weight at birth ***(Saker et al., 2008).***

A poor dietary intake of antioxidant nutrients or a low body level may be particularly important because recent evidence indicates that maternal oxidative stress during

pregnancy plays an important role in the pathophysiology of low birth weight. Therefore, antioxidant vitamins, such as vitamins C and E, may play a role in fetal growth ***(Lee, et al., 2004).***

Vitamin C or ascorbic acid is a hydro-soluble lactones (synthesized from glucose) essential to human body for several functions. Unlike many other animal species, humans and primates lack the terminal enzyme in the biosynthetic pathway for ascorbic acid synthesis, so diet is crucial for its availability in these organisms ***(Hans and Edward, 2010).***

Vitamin C counteracts several hydroxyl radicals and may contribute in protecting the fetus from oxygen free radical damage. On the other hand, it is known that vitamins C and E act synergistically against oxidative stress, worth noting that vitamin C is involved in the regeneration of oxidized vitamin E ***(Lee, et al., 2004).*** Also vitamin C promotes endothelial cell proliferation during the inflammatory condition, inhibits endothelial cell apoptosis and lipid peroxide formation, and improves endothelial dysfunction. Lower plasma vitamin C concentrations are consistently reported in women with preeclampsia ***(Ahn et al., 2007).***

AIM OF THE WORK

The aim of this study is to estimate the antenatal maternal plasma vitamin C level & its correlation with cord blood levels and to detect its influence on the placental growth and neonatal outcome.

VITAMIN C
L- ASCORBIC ACID

Introduction

Vitamins are organic compounds which have to be obtained from the diet, either because an organism does not have the enzymes necessary to synthesize them or because it cannot produce them in sufficient quantities. Humans cannot synthesize vitamins A, B1 (thiamine), B2 (riboflavin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (foliate), B12 (cobalamin), E and K but are able to synthesize some vitamin B3 (niacin) and D. The last vitamin required by humans, vitamin C (ascorbic acid), is a special case in that this organic compound is synthesized by the large majority of vertebrate and invertebrate species ***(Drouin et al., 2011).***

Vitamin C is a water-soluble compound with anti-oxidant properties that protects living organisms against oxidative stress. It is also essential for collagen synthesis, which is why insufficient amounts of this vitamin lead to scurvy ***(Drouin et al., 2011).***

Humans and other primates have lost the ability to synthesize vitamin C as a result of a mutation in the gene coding for L-gulonolactone oxidase, an enzyme required for the biosynthesis of vitamin C via the glucuronic acid pathway. This

genetic disorder generated a need to obtain ascorbate from diet in humans and other higher primates; ascorbate became vitamin C ***(Mandl et al., 2009).***

The importance of vitamin C was first discovered in 1747. During the 16th century numerous sea voyagers died due to the disease known as scurvy. James Lind found that men suffering from scurvy were cured when given oranges and lemons and he published his findings in the Treatise of the Scurvy in 1753. He developed a hypothesis based upon the results he observed; although his ideas were incorrect, he was the first person to understand the importance of what would later be called vitamin C. These findings were not widely accepted by the rest of the world and scurvy continued to lead to wide spread death throughout the 19th century ***(Jacob, 1999).***

Finally, in 1907 scurvy was induced in lab animals and this opened a new opportunity to understand the disease. Around 1930 two scientists working independently isolated and published their findings on vitamin C. The men found that vitamin C prevented and treated scurvy. The term ascorbic acid was adopted to describe its ability to prevent scurvy. The vitamin was then synthesized in the laboratory during 1933 ***(Bucci, 1998).***

Synonyms

Antiscorbutic vitamin, ascorbate, ascorbic acid (AA), ascorbyl palmitate, calcium ascorbate, cevitamic acid, iso-ascorbic acid, l-ascorbic acid & sodium ascorbate.

Chemistry

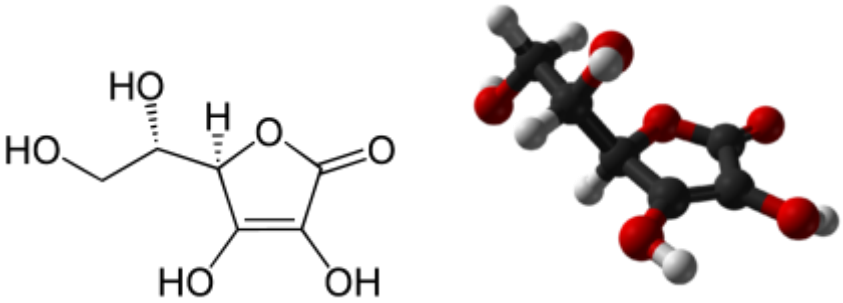

Fig. (1): Vitamin C (ascorbic acid) is six-carbon lactones that are synthesized from glucose in the liver of most mammalian species, but not by humans, Ascorbate is formed in the course of the uronic pathway starting from UDP-glucuronate in animals. Thus, its synthesis can be considered as an integral part of carbohydrate metabolism. ***(Mandl et al., 2009)***

Acidity

Ascorbic acid behaves as a vinylogous carboxylic acid where the electrons in the double bond ("vinyl"), hydroxyl group one pair, and the carbonyl double bond form a conjugated system. Because the two major resonance structures stabilize the deprotonated conjugate base of ascorbic acid, the hydroxyl group in ascorbic acid is much more acidic than typical hydroxyl groups.

In other words, ascorbic acid can be considered an enol where the deprotonated form is an enolate, which is usually strongly basic.

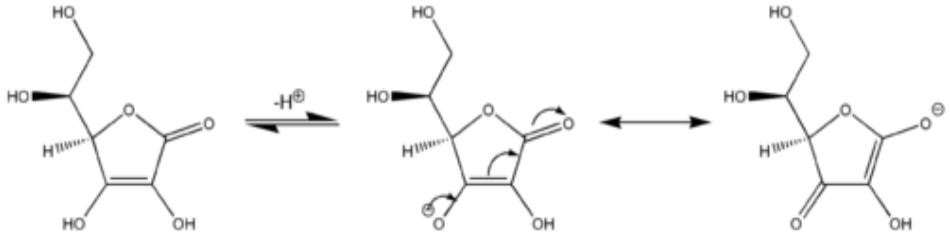

Fig. (2): Electron pushing for major resonance structures in conjugate base of ascorbic acid.

Enzymology

Enzymatic reactions are described for completeness. In humans, vitamin C acts as an electron donor for eight different enzymes ***(Levine et al., 2000).*** (will be discussed later in details).

At least for some of these enzymes, ascorbate adds electrons sequentially, with formation of the ascorbyl radical intermediate. ***(Prockop & kivirikko, 1995).***

In other reactions it add hydroxyl groups to the amino acids proline or lysine in the collagen molecule, thereby greatly increasing stability of the collagen molecule triple helix structure. ***(Rebouche, 1991).***

Biological significance

The biological role of ascorbate is to act as a reducing agent, donating electrons to various enzymatic and a few non-

enzymatic reactions. The one- and two-electron oxidized forms of vitamin C, semi-dehydroascorbic acid and dehydroascorbic acid, respectively, can be reduced in the body by glutathione and NADPH-dependent enzymatic mechanisms. The presence of glutathione in cells and extracellular fluids helps maintain ascorbate in a reduced state ***(Michels & Frei, 2012).***

Biosynthesis

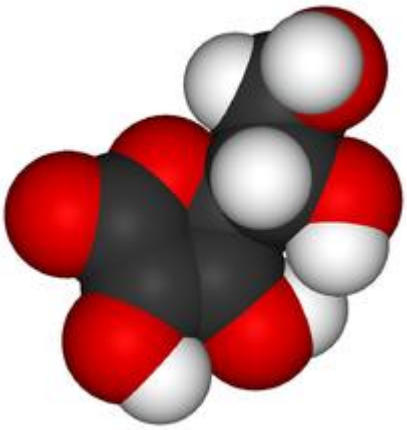

Fig. (3): Model of a vitamin C molecule. Black is carbon, red is oxygen, and white is hydrogen.

The vast majority of animals and plants are able to synthesize vitamin C, through a sequence of enzyme-driven steps, which convert monosaccharide to vitamin C. ***(Wheeler et al., 1998)***.

In some animals, glucose needed to produce ascorbate in the liver (in mammals and perching birds) is extracted from glycogen; ascorbate synthesis is a glycogenolysis-dependent process. In

reptiles and some birds the biosynthesis is carried out in the kidneys ***(Bánhegyi and Mándl, 2001).***

Humans and some animals lack the L-gluconolactone oxidase (GULO) enzyme, which is required in the last step of vitamin C synthesis, because they have a differing non-synthesizing gene for the enzyme (Pseudogene ΨGULO) ***(Harris & Robin, 1996).*** A similar non-functional gene is present in the genome of the guinea pigs and in primates including human . Some species (including humans) are able to make do with the lower levels available from their diets by recycling oxidised vitamin C ***(Montel-Hagen et al., 2008).***

Vitamin C in evolution

Venturi and Venturi ***(Venturi and Venturi, 2007)*** suggested that the antioxidant action of ascorbic acid developed first in the plant kingdom when, about 500 million years ago Mya (million years ago). Plants began to adapt to antioxidant-mineral deficient fresh-waters of estuaries ***(Purves et al., 1998).***

The terrestrial diet became deficient in many essential antioxidant marine micronutrients, including iodine, selenium, zinc, copper, manganese, iron, etc. Freshwater algae and terrestrial plants, in replacement of marine antioxidants, slowly optimized the production of other endogenous antioxidants such as ascorbic acid, polyphenols, carotenoids, tocopherols etc.,

some of which became essential "vitamins" in the diet of terrestrial animals (vitamins C, A, E, etc.) ***(Venturi and Venturi, 1999).***

It has been noted that the loss of the ability to synthesize ascorbate strikingly parallels the evolutionary loss of the ability to break down uric acid, also a characteristic of primates. Uric acid and ascorbate are both strong reducing agents. This has led to the suggestion that, in higher primates, uric acid has taken over some of the functions of ascorbate ***(Mandl et al., 2009).***

Absorption, transport, and disposal

Ascorbic acid is absorbed in the body by both active transport and simple diffusion. Sodium-Dependent Active Transport - Sodium-Ascorbate Co-Transporters (SVCTs) and Hexose transporters (GLUTs) are the two transporters required for absorption. SVCT1 and SVCT2 imported the reduced form of ascorbate across plasma membrane ***(Savini et al., 2008).*** GLUT1 and GLUT3 are the two glucose transporters and only transfer dehydroascorbic acid form of Vitamin C ***(Rumsey et al., 1997).***

Although dehydroascorbic acid is absorbed in higher rate than ascorbate, the amount of dehydroascorbic acid found in plasma and tissues under normal conditions is low, as cells rapidly reduce dehydroascorbic acid to ascorbate. Thus, SVCTs

appear to be the predominant system for vitamin C transport in the body ***(May et al., 2003)***

SVCT2 is involved in vitamin C transport in almost every tissue ***(Savini et al., 2008).*** The notable exception ,being red blood cells, which lose SVCT proteins during maturation ***(May et al., 2007).***

"SVCT2 knockout" animals genetically engineered to lack this functional gene, die shortly after birth***;*** suggesting that SVCT2-mediated vitamin C transport is necessary for life. ***(Sotiriou et al., 2002)***

With regular intake the absorption rate varies between 70 to 95%. However, the degree of absorption decreases as intake increases. At high intake (12g), fractional human absorption of ascorbic acid may be as low as 16%; at low intake (<20 mg) the absorption rate can reach up to 98% ***(young et al., 1996).***

Ascorbate concentrations over renal re-absorption threshold pass freely into the urine and are excreted. At high dietary doses (corresponding to several hundred mg/day in humans) ascorbate is accumulated in the body until the plasma levels reach the renal resorption threshold, which is about 1.5 mg/dl in men and 1.3 mg/dl in women. Concentrations in the plasma larger than this value (thought to represent body saturation) are rapidly excreted in the urine with a half-life of about 30 minutes; concentrations less

than this threshold amount are actively retained by the kidneys, and half-life for the remainder of the vitamin C store in the body increases greatly, with the half-life lengthening as the body stores are depleted ***(Oreopoulos et al., 1993).***

Although the body's maximal store of vitamin C is largely determined by the renal threshold for blood, there are many tissues that maintain vitamin C concentrations far higher than in blood. Biological tissues that accumulate over 100 times the level in blood plasma of vitamin C are the adrenal glands, pituitary, thymus, corpus luteum, and retina .Those with 10 to 50 times the concentration present in blood plasma include the brain, spleen, lung, testicle, lymph nodes, liver, thyroid, small intestinal mucosa, leukocytes, pancreas, kidney and salivary glands ***(Hediger, 2002).***

Ascorbic acid can be oxidized (broken down) in the human body by the enzyme L-ascorbate oxidase. Ascorbate that is not directly excreted in the urine as a result of body saturation or destroyed in other body metabolism is oxidized by this enzyme and removed **(*Hediger, 2002).***

Sources

Natural and synthetic dietary sources

The richest natural sources are fruits and vegetables. It is also present in some cuts of meat, especially liver. ***(Wilson, 2005).***

Vitamin C is the most widely taken nutritional supplement and is available in a variety of forms, including tablets, drink mixes, crystals in capsules or naked crystals ***(Wilson, 2005).***

Plant sources

Fruits and vegetables are the best sources of vitamin C (table 1). Citrus fruits, tomatoes and tomatoes juice, and potatoes are major contributors of vitamin C to the American diet ***(Institute of Medicine. food and nutrition Board, 2000).*** Other good food sources include red and green peppers, Kiwifruit, broccoli, strawberries, Brussels sprouts, and cantaloupes (table 1) ***(U.S. Department of agricultural research service, 2011) .***

Table (1): Selected food sources of vitamin C.

Food	Mg(mg)/ serving	%DV
Red pepper, sweet, raw, ½ cup	95	158
Orange juice, ¾ cup	93	155
Orange, medium	70	117
Grapefruit juice, ¾ cup	70	117
Kiwifruit, 1 medium	64	107
Green pepper, sweet, raw ½ cup	60	100
Broccoli, cooked, ½ cup	51	85
Strawberries, fresh, sliced, ½ cup	49	82
Brussels sprouts, cooked, ½ cup	48	80
Grapefruit, ½ medium	39	65
Broccoli, raw, ½ cup	39	65
Tomato juice. ¾ cup	33	55
Cantaloupe, ½ cup	29	48
Cabbage, cooked, ½ cup	28	47
Cauliflower, raw, ½ cup	26	43
Potato, backed, 1 medium	17	28
Tomato, raw, 1 medium	17	28
Spinach, cooked, ½ cup	9	15
Green peas, frozen, cooked, ½ cup	8	13

(U.S. Department of agricultural research service, 2011)

DV= Daily Value. DVs were developed by the U.S. Food and Drug Administration (FDA) to help consumers compare the nutrient contents of products within the context of a total diet. The DV for vitamin C is 60 mg for adults and children aged 4 and above. The FDA requires all food levels to list the percent DV for vitamin C. Foods providing 20%. Or more of the DV are considered to be high source of nutrient.

Animal sources

Vitamin C is most present in the liver and least present in the muscle. Since muscle provides the majority of meat consumed in the western human diet, animal products are not a reliable source of the vitamin. Vitamin C is present in human breast milk, but not present in raw cow's milk ***(Clark and Stephanie, 2007).***

Table (2): The following table shows the relative abundance of vitamin C in various foods of animal origin, given in milligram of vitamin C per 100 grams of food:

Animal source	**Amount (mg/ 100g)**
Calf liver (raw)	36
Beef liver (raw)	31
Oysters (raw)	30
Cod roe (fried)	26
Pork liver (raw)	23
Lamb brain (boiled)	17
Chicken liver (fried)	13
Lamb liver (fried)	12
Lamb heart (roast)	11
Lamb tongue (stewed)	6
Human milk (fresh)	4
Goat milk (fresh)	2
Cow milk (fresh)	2

(Clark and Stephanie, 2013)