The role of vitamin C as antioxidant in prevention of preeclampsia

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Abstract
The basis of the International Trial of Antioxidants for the Prevention of PE (INTAPP) study is based on the recognized role of oxidative stress in maternal PE syndrome. Some studies have shown that women with PE had lowered serum dosages vitamins E12, 13 and C14, 15, two powerful antioxidants. Antioxidants are molecules which, by interacting with reactive oxygen species (ROS), protect against the harmful effects of an excess of these molecules. Two studies conducted by Chappell et al. tend to show a beneficial effect of vitamin C supplementation in women at high risk of pre-eclampsia. The INTAPP study, for its part, is a multicenter study which aims to verify the effect of vitamin supplementation on the incidence of PE. In fact, the general hypothesis of this study is to verify whether supplementation with vitamins C in pregnant women can prevent the onset of PE. For this thesis, we hypothesized that A) the plasma concentrations of vitamins coenzyme Q10 (CoQ10) could vary during pregnancy, as much in women supplemented with vitamins C as in women not supplemented, and B) that the plasma levels of these antioxidants may be affected in women who develop PE compared to women who remain normotensive.

Keyword: complication, pregnant women, hypertension, preeclampsia

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Introduction
One of the most common complications in pregnant women is hypertension in pregnancy. We talk about hypertension when the systolic blood pressure is at least 140 mm Hg or the diastolic is at least 90 mm Hg and this, measured on two occasions at least 4 hours apart. There are 4 categories of pregnancy hypertension: chronic hypertension, gestational hypertension, PPE superimposed on chronic hypertension. Chronic hypertension is defined as hypertension that appears before the 20th week of pregnancy or persists beyond 12 weeks after delivery. Women who have high blood pressure, first detected after the 20th week of pregnancy, and who do not have proteinuria, are classified as having gestational hypertension. In addition, these women must return to normal pressure before the 12th week postpartum. PE syndrome is diagnosed when hypertension is observed after 20 weeks of pregnancy in a previously normotensive woman, and this is accompanied by significant proteinuria (> 0.3g of protein on a 24-hour urine collection). Finally, PE may develop in a woman with chronic hypertension. In this case, the prognosis of the mother and the fetus is worse than when the patient has only one of the two pathologies.

Definition of preeclampsia
PE is a multi-system disorder of unknown cause that occurs only during pregnancy in humans. It is a dangerous, common, difficult to predict and highly variable complication in the second half of pregnancy, childbirth and the postpartum period. In the past, edema was considered to be one of the clinical signs of this syndrome, but at present only hypertension and proteinuria are sufficient for diagnosis. Indeed, edema is not a specific symptom of preeclampsia since it also occurs during normal pregnancies and that some women suffering from PE have few or no. The presence of the placenta is necessary and sufficient to cause this disorder. On the other hand, a fetus is probably not required for PE to occur since cases of PE have been observed in the presence of hydatidiform mole. The underlying fetal and maternal mechanisms of preeclampsia are still not well understood. However, endothelial dysfunction is suggested as the link for several of the manifestations. The clinical signs of PE can manifest as well in the mother (hypertension and proteinuria with or without other multi-system abnormalities) as in the fetus (restriction of growth of the fetus, decrease in amniotic fluid and abnormal oxygenation). According to current definitions, there is a mild and a severe form of PE. As
defined above, PE is diagnosed when hypertension and proteinuria appearing after 20 weeks of pregnancy in previously normotensive women. It is then said to be a light PE.25. PE is considered to be severe when hypertension is severe, that is to say when the systolic pressure is at least 160 mm Hg or the diastolic pressure is at least 110 mm Hg and this, observed on two occasions, or when there is high blood pressure associated with one or more signs or symptoms such as: high proteinuria (≥5 g of protein per day), pulmonary edema, oliguria (<500 mL 24 hours), thrombocytopenia (<100,000 platelets / mm3), neurological signs or symptoms, epigastria pain or HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets).

**Etiology**

Cells are normally exposed to ROS that comes, among other things, from physiological processes related to energy transfer. ROS are very reactive molecules made up of at least one oxygen atom, such as the superoxide anion, nitrogen monoxide, hydrogen dioxide. These are key molecules in several physiological processes, as is the case, for example, in female reproduction.24. Oxidative stress occurs when the balance between the formation of ROS and the ability to neutralize these by antioxidants (superoxide dismutases [SOD], catalases, glutathione peroxidases and antioxidant vitamins) is in favor of ROS. This phenomenon is involved both in pathologies linked to aging and in many conditions such as atherosclerosis, ischemia-reperfusion injuries, inflammatory and neurodegenerative conditions.28. Recent studies tend to show that the imbalance between ROS and antioxidant defenses could also move the leading roles in a etiologies of PE. It is generally accepted that the development of PE can be done in two stages. First, there is an inadequate invasion of the trophoblasts of the spiral uterine arteries, which leads to poor placentation.11. This phenomenon occurs in the first, or early, second trimester of pregnancy and is considered to be the first step in the development of PE. Abnormal placentation would subsequently lead to periods of ischemia, thus creating increased production of ROS and secretion into the maternal circulation by the cytokine placenta, causing activation and generalized dysfunction of the endothelium.21. This is actually the 2nd step in the development of the PE. It is at this point that clinical manifestations characterizing the disease in the mother, such as hypertension and proteinuria, appear. This is because of the increased formation of vasoconstrictor factors (Endothelin, thromboxane, serotonin and superoxides), the increase in endothelial sensitivity to angiotensin II and the decrease in the production of vasodilator substances (nitric oxide, prostacyclins) that these phenomena occur.7. In addition, this dysfunction of the maternal vascular endothelium is responsible for impaired reactivity, vascular activity, activation of the coagulation cascade, loss of vascular integrity and multi-systemic damage that occurs during PE10. Many hypotheses about the etiology of PE have been raised. However, so far, four of them have caught our attention. The first is that involving placental ischemia which can cause endothelial dysfunction in the maternal organism. The second is the hypothesis suggesting the increased toxicity of very low density lipoproteins (VLDL) during pregnancy. The third is that there is a poor immune adaptation leading to an incomplete implantation of the spiral arteries and the last discusses a genetic predisposition involving the expression of a recessive gene or that of a dominant penetrating gene incomplete. According to the same authors, it would be possible to observe more than one of these mechanisms concurrently in a patient34.

**Complications in the mother and the fetus**

The maternal and perinatal consequences of PE depend on one or more of the following: the gestational age at the time of the disease, the severity of the disease, the quality of care the mother receives or absence of pre-existing medical disorders.22. In general, maternal and perinatal manifestations are not very damaging in women with mild PE which manifests itself beyond 36 weeks of pregnancy.2 On the other hand, morbidity and mortality, both in the mother and the fetus, increase in women who develop this disorder before the 33rd week of pregnancy. In the mother, the main complications of PE are eclampsia, cerebral hemorrhage, Abruptio Placenta, disseminated intravascular coagulation, HELLP syndrome, liver hemorrhage, and pulmonary edema, respiratory distress syndrome in adults, acute renal disorders and mortality. In addition, in the long term, these women are at risk of chronic hypertension, diabetes mellitus, chronic kidney disorders, heart disease, premature death. Indeed, several studies have shown that women who developed PE during pregnancy have an increased risk of cardiovascular complications in their future lives.4 In the fetus, we speak rather of intrauterine growth retardation, prematurity with associated complications (respiratory, neurological), hypoxia, acidosis and perinatal death. PE is responsible for about 25% of all very low birth weight children.50. In the long term, they are at risk for chronic lung disease, premature retinopathy, cerebral palsy, mental retardation as well as diseases in adulthood such as cardiovascular disease, PE or diabetes mellitus. About 60% of children born to a pre eclamptic mother have learning disabilities and have a low intelligence quotient (IQ).
Epidemiology
The incidence of PE between 1987 and 2004 in the United States averaged 27.4 cases per 1,000 deliveries52. This rate represents a significant increase of 24.6%. The incidence was 23.6 in 1987-1988 and it increased to 29.4 in 2003-2004. Regarding eclampsia, an average rate of 0.92 per 1000 deliveries has been reported.Unlike PE, a decrease in the rate of eclampsia was observed (1.04 during 1987-1995 to 0.82 during 1996-2004). According to a recent study53, 14.7% of women who suffered from PE during their first pregnancy were diagnosed with pre-eclampsia during their second pregnancy, while only 1.8% of women had PE when they had not suffered from it previously. It has also been shown that the risk of recurrence is around 12% for those who gave birth at full term in their first pregnancy, while the rate rises to 40% in women who have given birth at the 28th week of gestation or less.

Risk factors
This multi-systemic pregnancy disorder is seen more frequently in female and, the date PE, chronic hypertension, and multiple pregnancy as well as in women with an abnormality of the uterine artery detected by a Doppler scan 54. The mother's body mass index (BMI) before pregnancy would also be a factor to consider since the risk of developing PE increases with a high BMI55. In addition, prim parity (woman expecting her first child) is a significant risk factor since approximately 3 times more cases of PE occur during a first pregnancy. There is much evidence to suggest that PE is undoubtedly related to placenta. Its central position in the pathophysiology of PE has been demonstrated by cases of PE occurring in the presence of pregnancy defects such as hydatidiform moles22, 24, and ectopic pregnancies58. Multiple pregnancies also confer a 2- to 4-fold increased risk of PE59-61. What these complications have in common is the increased placental volume.

Prevention and treatments
The only effective treatment that can stop the symptoms of PE remains, to this day, childbirth. However, in recent years, several groups of researchers have attempted to find various theory to reducinga rat of PE. Briefly, there have been a few studies that have evaluated the effects of protein and salt restriction, supplementation with zinc, magnesium, fish oil and vitamins C, used diuretic with another antihypertensive drug PE17. Here we will only discuss methods that seem to have a potentially protective effect, i.e. calcium supplements, low doses of aspirin, and vitamin C supplements.

Calcium supplements
Some trials have shown that calcium supplementation (≥1g / day starting before the 35th week of pregnancy) reduces the risk of high blood pressure, Pmaternal death or serious morbidity but increases the risk of HELLP66 syndrome. The benefits of calcium were greater in women at high risk for hypertensive pregnancy disorders and in those with low calcium consumption. However, the lack of benefit from calcium in a large study68 had the effect of decreasing the used of Vet C in development country.

Low doses of aspirin
Thromboxane A2 is considered a potent vasoconstrictor, while prostacyclin is considered a vasodilator. It has been hypothesized that treatment with low doses of aspirin could inhibit the synthesis of thromboxane A2 and alter the balance in favor of prostacyclin, preventing the development of PE71. However, review authors conclude that the effects of consuming aspirin to prevent PE are weak. Indeed, again, another large study showed that there was no beneficial effect associated with this treatment.

Table (1): Publish study assesses the effect of vit C supplementations in preventions of preeclampsia

<table>
<thead>
<tr>
<th>Studies</th>
<th>Recruitment (week of gestations)</th>
<th>Dosage /24h</th>
<th>Vit C form</th>
<th>Plasmatic dosages</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chappell 72 (n = 284)</td>
<td>18–24</td>
<td>400 IU vit C + 1000mg vita E</td>
<td>Natural sources vita E</td>
<td>ok</td>
<td>Reductions in risks of preeclampsia’s</td>
</tr>
<tr>
<td>Beazley.85 (n = 100)</td>
<td>23–30</td>
<td>411 IU vit C + 1000mg vita E</td>
<td>not described</td>
<td>no</td>
<td>no effect</td>
</tr>
<tr>
<td>Rumbold.86 (n = 1877)</td>
<td>26–24</td>
<td>411 IU vita C + 1000mg vita d-to copherolsuccinate</td>
<td>no</td>
<td>no effects</td>
<td></td>
</tr>
<tr>
<td>Poston.81 (n = 3162)</td>
<td>26–32</td>
<td>411 IU vita C + 1000mg vita</td>
<td>OK not 100%</td>
<td>not reductions in PE danger use,</td>
<td></td>
</tr>
</tbody>
</table>
**Vitamin C supplements**

Knowing that oxidative stress is most likely involved in the disease process, researchers wanted to verify the effect of taking vitamin C supplements during the second half of pregnancy (weeks 16 to 22) in patients at high risk of developing PE17. They found, in fact, that this supplementation could be beneficial in preventing PE via the reduction of oxidative stress18. However, the administration of these same antioxidants once the disease has been established has no beneficial effect; The effects of supplementation with vitamins C will be discussed at greater length in section 3.2 of this thesis.

**General**

There are 2 types of antioxidants in the human body: enzymatic and non-enzymatic antioxidants. Enzyme antioxidants neutralize excess ROS and prevent damage to cellular structures. Superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and glutathione reductase are good examples. In the family of non-enzymatic antioxidants we find among others, glutathione (GSH) as well as vitamins and minerals like vitamin C, selenium, zinc, taurine, hypotaurine, glutathione, carotencarotene.

**Coenzyme Q10**

In addition to its role in the respiratory chain of mitochondriaCoQ10 have antioxidant effects on plasma lipoproteins. In fact, the reduced form of CoQ10 is believed to be one of the most potent inhibitors of low density lipoprotein (LDL) oxidation 79-81. Like vitamin E, CoQ10 is a reliable marker of oxidative stress82, 83. This coenzyme is also involved in several biological functions such as stopping the spread of free radicals by regenerating vitamin E84-88 or by reaction direct with ROS89. The average plasma concentration of CoQ10 is between 0.5 to 2 mol / L76. The reduced form of CoQ10 has been shown to be the first antioxidant to be oxidized in children and newborns when LDL particles are exposed to oxidative stress. In addition, it has been proposed that the ratio of oxidized / reduced CoQ10 could be a sensitive reliable marker for the study of disturbances in the redox balance, in the bloodstream decrease in plasma CoQ10 levels has been reported in people with conditions associated with oxidative stress as well as in women with PE92. This decrease is in line with the concept that fat-soluble antioxidants like vitamin Care less quickly affected by oxidative stress than CoQ1092.

**Vitamin C preeclampsia**

On the theoretical side, supplementation with antioxidant vitamins C plays an important role in reducing pre-eclampsia. In addition, this effect is in clinical practice. The simplification of the various studies in order to evaluate the effects of vitamin C supplementation in the prevention of precursors in table (1), 84 showed that vitamin C supplementation is of benefit in preventing pre-eclampsia in women who are developing diseases. However, in the large analysis, Poston failing to confirm like the protective roles for vitamins supplements, with they have confirmed and found that there has been an increase in cases of low birth weight children who have been exposed to vitamin supplements. Likewise, He conducts 68 clinical trials with couldn’t sure that vitamin C supplementations during pregnancy did a great role in reducing a risks of pre-eclampsia. Suggest that note of failure in theprotective effects may a fact that they began treatment early, a critical stage of the placenta (between 23 and 30 for 7 days gestations). Polis us current evidence has conclude that it supports the combined use of vitamin C supplements during pregnancy in order to obtain significant protection from pre-eclampsia, although the safety of these supplements in relation to infant outcomes is questionable. The differences in these reports may relate to the bioavailability of vitamin C among aparatipatefemalfe, variation in regulatory pathway of vitamins C, or another factor like thata form of vitamins C that is use in nutritional supplements. Know that after taking tocopherols the tocopherols active decrease, it is possible this tocopherols may has the great effects than tocopherols in order to reduce oxidation processes, it is recommended that vitamin C biform and its forms be provided in futures study, additionally, it is best to notes that in most studies publishing use vitamins supplements, plasma vitamin C level haven’t been determining.

**Conclusion**

Recent studies, in many of them, have failed to assess the effects of tocopherols supplementation on showing protective effects, while other studies and in a few of them have found harmful effects. Noting that supplementation with tocopherols as it reduces tocopherols levels, which they consider a form of vitamin C with a significant protective effect. It is likely that supplementing with tocopherols not the best antioxidant measure, on the other hand, vitamin C is necessary for the physiology of the natural reproductor organ, that the determination of the ideal relationship of dose hasn’t been completed. In order for the effect of vitamin C exposures to be properly evaluated, there is a demand for studies linking tissues to physiological indicators of tonomer and plasma levels. It’s possible that vitamins C supplementations are effective with in demand just when bio availability is reduce, in addition to that,
more researches are need to ascertains whether vitamins C supplements are just or are combined and combined and another supplement through pregnancy that should be beneficial to the health of the infant and mother. It will also be useful to determine whether it was previously found among mothers from a low birth weight supplement with vitamin C possibly linked to the low bioavailability of vitamin C.

Reference
