

Vitamins E, A and B₂ as Possible Risk Factors for Preeclampsia – under Consideration of the PROPER Study (“Prevention of Preeclampsia by High-Dose Riboflavin Supplementation”)

Vitamine E, A und B₂ als mögliche Risikofaktoren für Präeklampsie – unter Berücksichtigung der PROPER-Studie („Prevention of Preeclampsia by high dose Riboflavin Supplementation“)

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Abstract

In the course of the prospective, randomized, double-blind trial the influence of a high-dose riboflavin substitution on the risk for preeclampsia was studied in a high-risk collective [1]. The present contribution evaluates supplementary data from the already published PROPER trial. The patients were from the two study centers Mérida, Venezuela, and Moshi, Tanzania, they were randomized from the 20th week of pregnancy and received either 15 mg riboflavin daily or placebo. Clinical and laboratory checks were carried out at four-week intervals up to childbirth. Concerning the question of whether there is a relationship between the serum levels of antioxidative vitamins and the risk of developing preeclampsia, it was found that no relationship could be detected between the measured laboratory values of vitamins E, A and B₂ and the total risk of developing a hypertensive disease of pregnancy. On comparisons between patients with severe preeclampsia, those with a mild form, and the general healthy population, however, significant differences in the levels of antioxidative vitamins E and A as well as the FAD level were seen. The patients from Tanzania showed on the whole significantly lower vitamin levels than those from Venezuela, possibly due to the better nutritional situation in Venezuela. Considering the results altogether, the role of antioxidative parameters in the pathophysiology of preeclampsia remains unclear. However, the collected data provide valuable hints for future preventative strategies.

Zusammenfassung

Im Rahmen der prospektiven, randomisierten, doppelt-blinden Studie wurde der Einfluss einer hoch dosierten Riboflavinsubstitution auf das Präeklampsierisiko in einem Hochrisikokollektiv untersucht [1]. Die vorliegende Arbeit wertet hierzu ergänzende Daten aus der bereits publizierten PROPER-Studie aus. Die Patientinnen stammten aus den beiden Studienzentren Mérida, Venezuela, und Moshi, Tansania, wurden ab der 20. SSW randomisiert und erhielten entweder 15 mg Riboflavin täglich oder Placebo. Bis zur Entbindung erfolgten klinische und laborchemische Kontrollen in 4-wöchentlichem Abstand. Zur Klärung der Frage, ob ein Zusammenhang zwischen Serumspiegeln antioxidativer Vitamine und dem Risiko, an Präeklampsie zu erkranken, besteht, zeigte sich, dass das Gesamtrisiko, eine hypertensive Schwangerschaftserkrankung zu entwickeln, keinen Zusammenhang mit laborchemisch gemessenen Vitaminspiegeln E, A und B₂ erkennen ließ. Beim Vergleich zwischen Patientinnen, die an schwerer Präeklampsie erkrankten, mit leichten Formen und der gesunden Kontrollpopulation fanden sich allerdings signifikante Unterschiede in der Höhe der antioxidativen Vitamine E und A sowie der FAD-Spiegel. Patientinnen aus Tansania zeigten insgesamt signifikant niedrigere Vitaminspiegel als Schwangere aus Venezuela, möglicherweise bedingt durch eine bessere Ernährungssituation in Venezuela. In Zusammenschau der Ergebnisse bleibt die Bedeutung antioxidativer Parameter in der Pathophysiologie der Präeklampsie weiterhin unklar. Die erhobenen Daten liefern jedoch wertvolle Informationen für zukünftige Präventionsstrategien.

Introduction and Aims

Preeclampsia is the most common cause of maternal death in the industrialized countries and makes a major contribution to perinatal mortality and morbidity [2]. The worldwide incidence of preeclampsia is between 2 and 10%. According to WHO estimations the disease occurs up to 7 times more often in the developing countries than in the industrialized nations [3]. There are practically no valid data on the prevalence in South America, in some African countries preeclampsia occurs in up to 17% of all pregnancies [3].

The clinical picture of preeclampsia is based on a generalized endothelial dysfunction, but the exact triggering factors are still unknown [2]. Oxidative stress and the thus formed lipid peroxides are considered to cause damage to the membranes of endothelial cells [4,5]. As the result of a placental hypoxia, induced by immunological factors, surface placentation, or intrinsic factors of pregnancy (twin pregnancy, polyhydramnios), an increased formation of free radicals and lipid peroxides occurs in the placenta [6,7]. Leukocytes are subsequently activated and released from the placenta into the systemic circulation [8], these in turn induce the liberation of cytokines in the maternal organism and initiate a generalized inflammatory reaction [9,10] that can only be controlled by cellular antioxidative systems. The peripheral vasoconstriction as well as the reduced placental perfusion occurring in preeclampsia are additionally reinforced by inactivation of the vasodilatory NO synthetase system [11] as well as the shift of the PGI_2 - TXA_2 ratio in favor of thromboxane A_2 . Aggressive lipid peroxides are thereby responsible for an increased activation of cyclooxygenases which, in turn, induce an increased production of free radicals. The increased tendency for thrombocyte aggregation in preeclampsia can also be explained by the increased formation of thromboxane A_2 [12].

In the serum of women with preeclampsia the levels of antioxidative vitamins are reduced due to the increased oxidative stress with elevated consumption of antioxidative valences [13]. Substitution of antioxidative vitamins in patients with preeclampsia, however, has remained unsuccessful and this can be indicative of a too far advanced disease process [14]. When therapy is started in the 20th week of pregnancy, however, substitution with the antioxidative vitamins E and C can achieve a significant reduction in the number of preeclampsia cases [15].

Already published results of the PROPER trial indicate a possibility for prevention of preeclampsia in a high-risk collective by isolated, high-dose substitution of riboflavin [1]. The present contribution examines as a supplement the influence of the antioxidative vitamins E, A and B_2 in the serum or, respectively, whole blood of pregnant patients from the PROPER study (PROPER – prevention of preeclampsia with riboflavin) in respect to the risk of developing preeclampsia. Here, two different study populations (pregnant women from Tanzania or Venezuela) were each compared with a healthy control population. Primary endpoint of the trial was the question if and at which time point during the pregnancy do the mentioned micronutrients have an effect on the risk to develop preeclampsia. Secondary endpoint was, besides a description of the vitamin levels during pregnancy, especially the effect of daily riboflavin substitution on the serum levels of antioxidative vitamins.

Materials and Methods

Patients

The study was performed between 2002 and 2005 at the two study centers in Venezuela and Tanzania. Approval was granted by the responsible ethic commissions.

In the first study center in Mérida, work was done in cooperation with the semi-governmental PPP, program for the prevention of preeclampsia [17], in which pregnant patients at risk for preeclampsia were globally recorded and transferred to corresponding referral centers of the program. Altogether 414 women were recruited.

The 2nd center in Moshi, Tanzania was represented by the Kilimanjaro Christian Medical Center, KCMC. Because of the markedly lower global recording of risk patients and the difficult infrastructure, only 41 patients were enrolled in the study in Tanzania; however due to the monocentric structure there was a minimal drop-out rate.

Randomization

Enrollment of pregnant women in the trial was possible up to the 20th week of pregnancy upon fulfillment of the 2 inclusion criteria (1) primigravida or (2) multigravida with a hypertensive disease in the preceding pregnancy. Each patient received a structured explanation in her native language.

Trial participants were continuously randomized and assigned by chance to a riboflavin or a placebo group. Randomization was done according to the block system that ensured that out of 10 enrolled patients 5 from each group were present. The assigned numbers of each patient were derived from a continuous code based on time of entry into the trial.

Study medication

The study medications were prepared exclusively for the present study. Sealed medication boxes that contained either the study medication or the placebo were printed with the corresponding randomization codes. These were given to the patients at each visit for the next four weeks. The patients were examined and questioned according to the study protocol at four-week intervals up to the 37th week of pregnancy and then weekly until delivery. An independent study coordinator carried out the blinding at the end of the study. When entering the trial at the 20th week of pregnancy each patient received, depending on the randomization, 15 mg riboflavin daily or an identical looking placebo preparation.

Performance of the study

At each visit, besides data registration by means of a questionnaire, plasma samples of venous blood and, respectively at the time of delivery also umbilical cord blood were taken and stored at -20°C in the dark until analyzed. Determinations of the plasma levels of FAD (flavin adenine dinucleotide), vitamin E (tocopherol) and vitamin A (retinol) were made by HPLC (high performance liquid chromatography) using standard procedures [18].

A trial participant was classified as hypertensive when a diastolic blood pressure of greater than 90 mmHg or a systolic blood pressure of greater than 140 mmHg was measured, or a relative increase of the diastolic blood pressure of more than 15 mmHg or of the systolic blood pressure of more than 30 during the pregnancy was observed. Preeclampsia was diagnosed when, in addition to the hypertension, a significant proteinuria of more than 300 mg/L according to the dip-stick test was seen. A severe preec-

lampsia was recognized when additional neurological symptoms such as, for example, flickering vision, hyperreflexia, eclampsia, or when a diastolic blood pressure of greater than 110 mmHg was measured.

Statistics

The statistical evaluation was performed using SPSS for Windows, Version 10.0. In cooperation with the Department of Biometry, Faculty of Mathematics, University of Heidelberg, above all, average value comparisons for independent random samples (Student's *t* test), the χ^2 test and unifactorial ANOVAs were undertaken. *P* values < 0.05 were considered as significant.

Results

Altogether in all study centers, a total of 455 patients were recruited and randomized. The Venezuelan contribution to the study comprised 414 patients compared to the 41 participants from Tanzania, i.e. 10-fold more.

In Venezuela patients were enrolled into the study already in the 12th week of pregnancy whereas those in Tanzania were first recruited from the 20th week. Furthermore, the two collectives differed in the number of recruited primigravidas, the proportion in Venezuela of 55.2% was markedly lower than that in Tanzania with 87.8%. Accordingly, the number of previous pregnancies with on average 1.9 per patient was markedly higher than that in the collective examined in Tanzania (on average 1.1 pregnancies). Altogether 13.3% of the patients showed symptoms of a hypertensive disease of pregnancy, in Tanzania with 12.2% negligibly less than in Venezuela with 13.5%. 49.9% of the participants received placebo, 50.1% the study medication riboflavin at a daily dose of 15 mg from the 20th week of pregnancy.

In the entire collective the drop-out rate was 12.5%. In Venezuela the drop-out rate was 13.5%, markedly higher than that of the smaller Tanzanian collective, among whom merely 2.4% of the patients failed to appear for the first follow-up examination.

Prevalence of preeclampsia

In Venezuela and Tanzania the proportions of the patients who developed preeclampsia (PE) or pregnancy-induced hypertension were statistically not different (Table 1).

However, on subgroup analyses of the hypertensive diseases in various degrees of severity, there was a marked discrepancy between the two countries with regard to preeclampsia: severe forms of the disease occurred in 4.2% in Venezuela (10 cases) whereas such severe forms of the disease were not observed in Tanzania. In addition, one case of eclampsia was observed in the Venezuelan collective.

Vitamin E

Altogether 505 individual determinations of vitamin E from the serum of pregnant women at consecutive time points were made; this corresponds to a total number of 107 completely analyzed participants. Thus, on average, 4.72 determinations per patient at 4-week intervals were performed. In addition, analyses of 26 umbilical cord serum samples originated from this collective. The vitamin E levels showed on the whole an asymptotic rise up to a maximum in the 38th week and then a decrease to delivery time and a further decrease thereafter (40+). The umbilical cord values for vitamin E amounted to $\frac{1}{3}$ – $\frac{1}{4}$ of the maternal values (Fig. 1).

Table 1 Frequency distribution of the varying degrees of severity of hypertensive diseases of pregnancy in patients of the PROPER study.

	Pregnancy-induced hypertension (PIH) (%)		Preeclampsia (PE) and eclampsia (%)	
	mild	severe	mild	severe
Total collective n = 455	5.3		8.0	
	4.7	0.7	4.4	3.7
Venezuela n = 414	5.4		8.1	
	4.6	0.8	3.8	4.2
Tanzania n = 41	4.9		7.3	
	4.9	0.0	7.3	0.0
Signif. level	n. s.	n. s.	n. s.	p < 0.01

n. s.: not significant; χ^2

In a comparison of the two countries, all patients from Venezuela exhibited significantly higher vitamin levels than the comparable collective from Tanzania ($p < 0.05$ for 24th, 28th and 38th weeks). There were no differences between the two collectives in umbilical cord blood (Fig. 1).

At no time during pregnancy could a significant relationship between the measured vitamin E levels and the risk for developing a hypertensive disease of pregnancy be deduced. In the subgroup analysis of the different degrees of severity of the hypertensive diseases of pregnancy, however, it was found that the vitamin E levels of patients with severe preeclampsia were markedly elevated, especially from the 20th to 28th week when compared with all other patients (those with mild forms of disease and healthy controls). A significant result was seen for the 28th week of pregnancy ($p < 0.05$, Fig. 2). In particular, decreased vitamin levels were seen in those patients who developed a mild form of preeclampsia or an SIH, even when compared to healthy patients. All other serum levels were in the pregnancy-related normal range of a healthy control group (Fig. 2).

In comparison to the placebo group, the riboflavin supplementation from the 20th week of pregnancy had no influence on the level of vitamin E in serum either during pregnancy or in umbilical cord blood (data not shown).

Vitamin A

Altogether 504 individual determinations of vitamin A were made for 109 completely analyzed participants, corresponding to 4.62 determinations per patient. In addition, analyses of umbilical cord serum samples for vitamin A were performed for 36 patients.

In the entire collective of women from both countries the vitamin A level increased up to the 24th week of pregnancy, remained rather constant to the 40th week and decreased again upon delivery. The umbilical cord values amounted together to $\frac{1}{3}$ – $\frac{1}{2}$ of the maternal values. Maternal vitamin A levels in the entire collective thus exhibited on the whole a decreasing tendency (Fig. 3).

In a comparison between the countries, as also seen in the case of vitamin E, the vitamin A levels of the patients from Tanzania were significantly lower throughout the pregnancies (Fig. 3). Only in the 40th week of pregnancy did the vitamin A level of the Venezuelan patients fall below that of the Tanzanian patients, albeit with their small number.

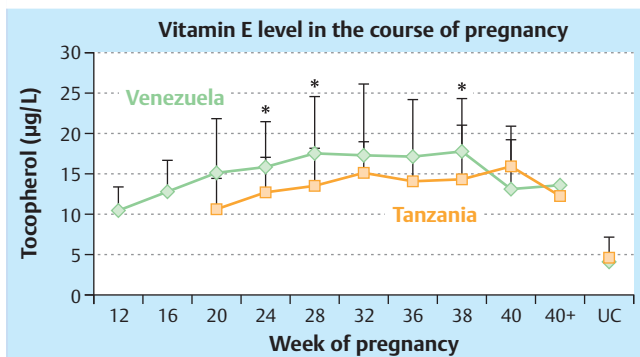


Fig. 1 Mean values with STD. Vitamin E in the course of pregnancy – country comparison. UC: Umbilical cord; Vitamin E level in µg/L; n = 505; t-test; * p < 0.05

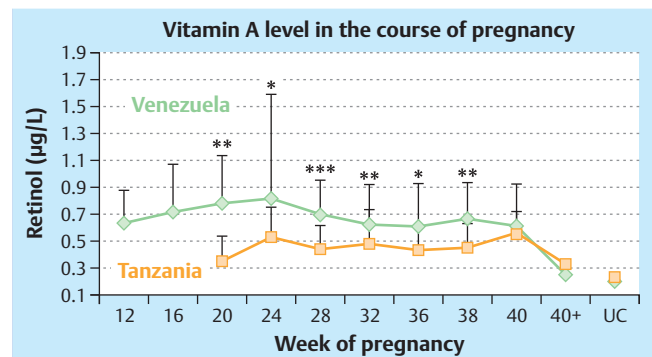


Fig. 3 Mean values with STD. Vitamin A in the course of pregnancy – country comparison. UC: Umbilical cord; Vitamin A level in µg/L; n = 504; t-test; * p < 0.05; ** p < 0.01; *** p < 0.005

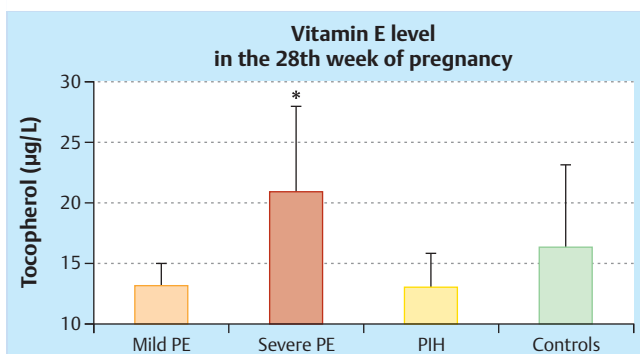


Fig. 2 Mean values with STD. Vitamin E 28th week of pregnancy according to degree of severity of preeclampsia (PE) and controls. Vitamin E level in µg/L; n = 107; t-test; * p < 0.05

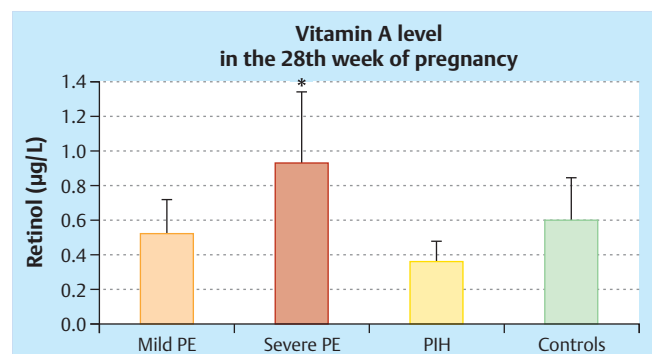


Fig. 4 Mean values with STD. Vitamin A 28th week of pregnancy according to degree of severity of preeclampsia (PE) and controls. Vitamin A level in µg/L; n = 109; t-test; * p < 0.05

At no point in time could a relationship be found between the measured vitamin A levels and the risk to develop a hypertensive disease of pregnancy. Subgroup analyses of the different degrees of severity of the hypertensive diseases of pregnancy, however, did show markedly higher vitamin A levels between the 20th and 28th weeks of pregnancy in those patients with severe preeclampsia. Here also the result was significant in the 28th week ($p < 0.05$, Fig. 4).

The daily administration of 15 mg riboflavin had a positive impact on the magnitude of the vitamin A level between the 20th and 24th as well as in the 40th week of pregnancy.

Vitamin B₂

Flavin adenine dinucleotide (FAD) was determined as a marker for the flavin status. Altogether 456 individual determinations of FAD were made by HPLC, corresponding to 102 trial participants with on average 4.47 determinations per patient. In addition umbilical cord analyses were available from 39 patients.

During the entire course of pregnancy the FAD levels showed a relatively constant course with a slightly increasing value around the 36th week of pregnancy, a decrease around the 38th week and a renewed increase towards the end of the pregnancy being apparent only among the patients from Venezuela. The FAD levels in the Venezuelan collective were significantly higher than those in the patients from Tanzania. In contrast, the umbilical cord val-

ues from the Tanzania collective were on average higher than the maternal values (Fig. 5).

In contrast to the decrease in the umbilical cord levels of the antioxidative vitamins E and A compared to the maternal values, the vitamin B₂ levels in umbilical cord blood remained constant in both collectives or were even slightly higher than the maternal FAD levels in Tanzania.

In the 16th week – and thus before starting the study medication – the groups of patients who later developed preeclampsia (PE) or pregnancy-induced hypertension (PIH) exhibited significantly lower FAD levels in comparison to the healthy controls ($p < 0.05$). From the 20th week of pregnancy until delivery slightly elevated FAD levels were seen in the groups of patients who became ill compared to the control group. The FAD levels in umbilical cord blood did not show any differences.

When the FAD levels of those patients who developed severe preeclampsia or eclampsia were compared with those with merely mild forms of PE or PIH as well as those of healthy controls, markedly elevated levels and statistically significantly elevated levels of FAD were observed respectively in the 24th and 28th weeks of pregnancy for the group with severe preeclampsia ($p < 0.05$). No differences in the FAD levels between the two groups were observed at all other time points during pregnancy (Fig. 6).

On examination of the impact of daily riboflavin substitution on the actually measured FAD levels in whole blood in both centers, a clear correlation between the FAD level and the daily consump-

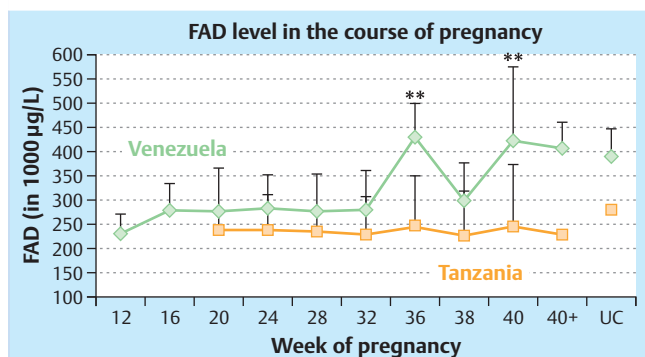


Fig. 5 Mean values with STD. Vitamin B₂ in the course of pregnancy – country comparison. UC: Umbilical cord. Vitamin B₂ level in µg/L; n = 456; t-test; ** p < 0.01

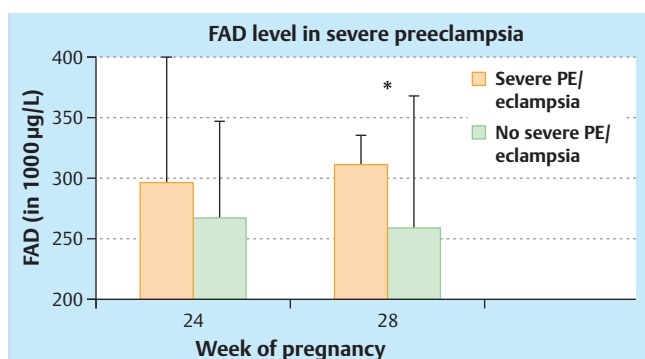


Fig. 6 Mean values with STD. Vitamin B₂ in severe preeclampsia in the 24th and 28th weeks of pregnancy compared with controls. Vitamin B₂ level in µg/L; n each per SSW = 102; t-test; * p < 0.05

tion of vitamin B₂ during the course of pregnancy was seen in the verum arm of the study, whereby the values in Tanzania increased even more strongly than those in Venezuela. From the 20th week of pregnancy the groups receiving riboflavin substitution uniformly exhibited higher FAD levels than the groups receiving placebo; this was also true for the FAD levels in umbilical cord blood (● Fig. 7).

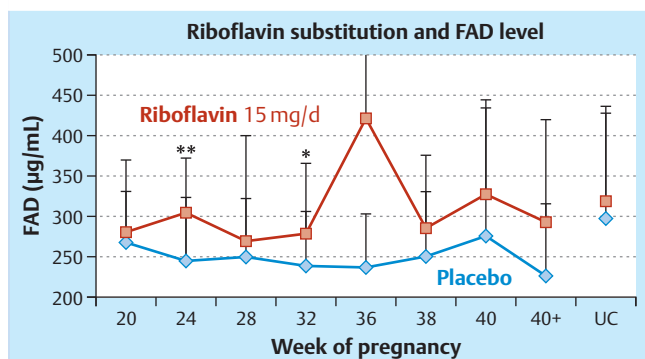


Fig. 7 Mean values with STD. Influence of riboflavin substitution on FAD level in the course of pregnancy. UC: Umbilical cord. Vitamin B₂ level in µg/L; n = 102; t-test; * p < 0.05; ** p < 0.01

Multivitamin preparations

Many patients reported the regular consumption of multivitamin preparations during their pregnancies. For those patients with additional vitamin substitution, an additive effect on the magnitude of serum levels could be detected in the examinations of the vitamin E and A levels. No such effect was seen on evaluation of the FAD levels. The contents of the additionally consumed preparations could not be examined further for logistic reasons.

Discussion

The results presented here at first reveal no correlation between the status of the antioxidative vitamins E, A und B₂ and the development of a hypertensive disease of pregnancy in the examined collectives. However, when the influence of the vitamin levels on the different degrees of severity of the preeclampsia are examined, significantly elevated parameters, above all around the 28th week of pregnancy, are found in the patients with severe preeclampsia and eclampsia in comparison with those patients with mild forms of disease and the healthy control group.

Chappell et al. [15] in 1999 reported for the first time on the possibility to prevent preeclampsia in a high-risk collective by administration of high doses of antioxidative vitamins including vitamin E. However, up to now no other groups have been able to repeat or confirm this finding.

In a randomized prospective study [19] the patients of a collective at risk for preeclampsia were treated from the 14th to 20th week of pregnancy onwards with high doses of vitamin E (400 IE/d) and vitamin C (1000 mg/d), a control arm received placebo. The study did not achieve the planned number of patients and in the actually evaluated collectives no significant benefit from the vitamin supplementation could be detected.

In a recent prospective substitution study by Poston et al. [20] also no preventative effects of vitamin A and E supplementation could be demonstrated. Furthermore, in a metaanalysis of the Cochrane Library [21, 22] 566 patients supplemented with vitamin E were evaluated but again no improvement in the pregnancy outcomes or preeclampsia rates were observed.

It has sporadically been reported that the measured levels of antioxidative vitamins (above all vitamin E) are even elevated in patients with preeclampsia. It has been discussed that this could be the result of a compensatory up-regulation. In an extensive study on oxidative stress in preeclampsia, Llorba et al. [2] proposed the hypothesis that oxidative stress in mild form does indeed participate in the pathogenesis of preeclampsia but cannot be considered as a relevant triggering factor of the disease. In particular, in this study the vitamin E levels of women with preeclampsia were elevated in comparison with those of normotensive controls, this was considered to be a physiologically reactive activation in generally increased oxidative stress.

At the beginning of 2006 Neugebauer et al. [23] reported about the impact of vitamin B₂ substitution on the risk of developing preeclampsia and found, in a prospective, randomized study of a collective of more than 800 pregnant women in Burkina Faso, no preventative effects of a daily supplementation of 15 mg riboflavin. However, in this study the total number of patients with the disease was very low (3.6%) and the degrees of severity of the preeclampsia were not mentioned.

It is of interest that in the present work a marked elevation of the investigated antioxidative markers was observed in the severe forms of preeclampsia whereas, in contrast, the mentioned vita-

min levels in mild forms of the disease were even lower than the levels of the healthy control collective at the examined time points during pregnancy. It is possible that a first extreme consumption of antioxidative valences, as occurs in severe preeclampsia, leads to an excessive counter-regulation by antioxidative valences, whereas in mild forms or in pregnancy-induced hypertension without proteinuria merely a consumption without a significant counter-regulation is observed. The question of if, prior to randomization of the patients to the corresponding study arms, possibly a correlation between the FAD level and high or low vitamin levels had already existed can, unfortunately, not be answered due to the small number of cases. Possible causes for the significant elevation of the FAD level in the 20th to 28th weeks of pregnancy in patients with severe preeclampsia could also be retention with limited renal function due to reversible organ damage in the course of the disease [24].

The choice of the study collective plays a decisive role for this question. Nutritional deficits only reach pathological relevance when extremely pronounced. Prevention by means of supplementation with antioxidative vitamins will only be successful in a population suffering from a pronounced deficit of such vitamins and thus an important proportion of the observed preeclampsia cases could be caused just by such a deficit of antioxidants.

Thus, the observed collective of women in Venezuela did not benefit from vitamin E and A substitution in the course of consumption of multivitamin preparations in regard to the frequency of preeclampsia. In Tanzania the measured vitamin levels were markedly below the levels of the Venezuelan collective, the influence of vitamin E and A substitution in relation to the consumption of multivitamin preparations could not be evaluated or, respectively, detected in this collective. This may possibly have led to a bias in the presented results.

The starting points for the administration of the study medication were chosen for practical reasons (many women in Venezuela and Tanzania do not attend for pregnancy care at earlier points in time). On the other hand, the second phase of trophoblast invasion in the maternal myometrium occurs at around the 20th week of pregnancy at which stage a riboflavin deficit can have pathogenetic relevance [16]. A toxicity of riboflavin during pregnancy has not been reported in the literature and maximum doses have not been mentioned. The dose of 15 mg/day was chosen to ensure a realistic high-dose supplementation.

Limitations of this study are, among others, the different numbers of worked-up samples for vitamin B₂ in comparison to vitamins E and A, probably due to differing transport conditions for the samples from the respective centers to Germany. Maintenance of the cooled state and protection from light were, however, ensured in all cases and the evaluation of all samples (Venezuela and Tanzania) was carried out under identical, standardized conditions at the Institute for Clinical Chemistry at Mannheim University Hospital. A further weak point of the study is certainly the different patient numbers at the two study centers. In particular the inclusion of the vitamin results of the much smaller collective from Tanzania in the total statistics could have induced a bias due to the differing basic situations of the two centers.

We consider the actually measured elevation of the FAD levels in the study groups to be a positive compliance control with regard to consumption of the study medication (● Fig. 7).

Even so, a high-dose vitamin B₂ substitution seems to have prevented some severe cases of preeclampsia in the investigated collectives. Concerning the question whether ultimately the daily

administration of high-dose riboflavin from the 20th week of pregnancy can prevent cases of preeclampsia, the results of the endpoint evaluation of the PROPER study must be awaited [1].

Facit



The utility of a general supplementation with antioxidants thus still remains an open question.

The results presented here add further support to the hypothesis that the pathogenesis of preeclampsia represents the end stage of various different disorders that all converge into a uniform clinical picture. The impact of isolated dysfunctions such as the isolated occurrence of vitamin E, A or B₂ deficits is probably small. Oxidative stress and antioxidative capacity involve the interaction of numerous factors and future preventative strategies should therefore ideally combine several antioxidative principles.

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Conflict of Interest



In the present article merely the biochemical serum parameters of antioxidative vitamins from patients of the PROPER study were analyzed. There is no conflict of interest with the main study and the authors are identical.

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