Trials Raise Flags on Vitamins C, E in Pregnancy

High dosages yielded no benefits for prevention of preeclampsia and increased risk of poor outcomes.

BY MITCHEL L. ZOLER
Philadelphia Bureau

LISBON — A metaanalysis of results from two major trials of prenatal supplementation with high dosages of vitamins C and E has raised concern about possible adverse effects, such as an increased risk of stillbirths and of gestational hypertension.

More stillbirths are "a worry, but it is an exploratory analysis. We'll need to look at the results from other studies" that are still in progress, Dr. Andrew H. Shennan said at the 15th World Congress of the International Society for the Study of Hypertension in Pregnancy.

Although results from the two recent trials—which together involved more than 4,000 women—showed that high dosages of vitamin C and E supplements had no benefit for preventing preeclampsia and may have caused harm, experts continued to endorse the underlying hypothesis that treatment with one or more antioxidant agents might prevent preeclampsia.

"There is a sound academic basis to think that oxidative stress plays a role in preeclampsia," said Dr. Lucilla Poston, a professor in the maternal and fetal research unit at King's College London, and co–principle investigator for one of the trials.

"We don't want people to go away thinking that this is the end of oxidative stress in preeclampsia. Preeclampsia is a very rapid situation, with accelerated oxidative stress. We need to think about [intervening at] the etiology of oxidative stress and the enzymes that produce superoxides," Dr. Poston said.

The Vitamins in Preeclampsia (VIP) trial enrolled about 2,400 pregnant women at week 14-21 gestational age who were at high risk for preeclampsia at 26 centers, 25 of them in the United Kingdom. The women were randomized to placebo or daily supplementation with 1 g vitamin C and 400 IU vitamin E daily through delivery. The high dosages of the two vitamins contrast with the content of a typical prenatal vitamin, which often contains 120 mg of vitamin C and 30 IU of vitamin E.

The primary end point was preeclampsia incidence. To qualify as high risk, women had to have at least one condition from a prespecified list that included a history of preeclampsia before 37 weeks in the preceding pregnancy, gestational hypertension, preconception diabetes, body mass index (kg/m^2) of at least 30 at first antenatal examination, renal disease, and abnormal uterine artery Doppler waveform analysis.

Preeclampsia occurred in 15% of women on the vitamin supplement and in 16% of those on placebo, a nonsignificant difference (Lancet 2006;367:1145-54).

James E. Reinaker/Elsevier Global Medical News

The VIP trial's high dosages contrasted with typical prenatal dosages, such as 120 mg of vitamin C or 30 IU of vitamin E.

The second trial reported in April was the Australian Collaborative Trial of Supplements (ACTS), which enrolled 1,877 pregnant women at 14-22 weeks gestational age who were at low risk for preeclampsia, at nine centers in Australia. The vitamin supplement dosages were the same as the dosages in the VIP trial; the primary outcomes were also similar. To focus on low-risk women, the study enrolled only nulliparous women with singleton pregnancies who were normotensive; the study also had other exclusion criteria. The average BMI of women in the study was 24.

The rate of preeclampsia was 6% in the supplement group and 5% in the control group, a difference that was not statistically significant (N. Engl. J. Med. 2006;354:1796-806).

Although results from both studies put to rest the idea of high-dosage prenatal vitamin C and E supplements, many pregnant women are currently taking these vitamins at high dosages, said Dr. Shennan, a professor of obstetrics at King's College London and the second principal investigator for the VIP trial. That fact is especially worrying given the suggestion of harm from these dosages in a metaanalysis that included the VIP and ACTS trials as well as two small, earlier studies. All four studies used the same supplement dosages, and they together involved more than 4,500 pregnant women.

Overall, women in the vitamin group had a roughly 50% higher rate of gestational hypertension, and a nearly twofold higher rate of both treatment with an antihypertensive agent and treatment with magnesium sulfate for preeclampsia, Dr. Shennan reported.

The rate of stillbirths was also twice as high in women who received vitamin supplements compared with those in the control group. All of the differences were statistically significant. ■

Placental *Ureaplasma* Infection Linked to Preterm Birth

BY BRUCE JANCIN
Denver Bureau

LISBON — Women who give birth prematurely have a markedly increased prevalence of placental *Ureaplasma urealyticum* infection, Dr. Leonard E. Weisman reported at the 12th International Congress on Infectious Diseases.

Detection of the infection prior to labor would permit timely antimicrobial therapy.

DR. WEISMAN

This novel observation raises the possibility that a significant fraction of preterm births might be preventable if a practical means of prospectively identifying women placentally colonized or infected with *U. urealyticum* can be developed. Their detection prior to labor would permit timely antimicrobial therapy aimed at clearing their placental infection—and deactivating their preterm birth trigger, Dr. Weisman explained in an interview.

This strategy would not provide a total answer to the enormous problem of preterm birth, which has a multitude of potential causes. But it would take a substantial bite out of the problem.

It has been estimated that reproductive tract infections play a role in up to 60% of all preterm births. Placental *U. urealyticum* probably figures in a substantial minority of those infections, said Dr. Weisman, professor of pediatrics at Baylor College of Medicine and director of the perinatal center at Texas Children's Hospital, Houston.

He presented a case-control study involving 58 women at three hospitals in the Texas Medical Center who gave birth at 30 weeks' gestation or earlier. The control group consisted of 194 randomly selected women who had a term birth. Twenty-seven women in the control group were classified as complicated controls, meaning they had a term delivery involving premature rupture of membranes, maternal fever, prolonged rupture of membranes lasting longer than 18 hours, and/or clinical endometritis or chorioamnionitis.

All study participants had their placental chorion cultured for *U. urealyticum* and group B streptococcus using sterile technique. The prevalence of *U. urealyticum* colonization/infection was significantly greater in women with preterm birth or a complicated term delivery than in those with an uncomplicated term birth (see box).

The medical literature describes numerous unsuccessful attempts to reduce the incidence of preterm birth via antibiotic therapy.

These past disappointments may have been due to reliance on easily assessable lower genital tract infection as the indication for treatment, when it's actually placental involvement that matters, Dr. Weisman said at the congress sponsored by the International Society for Infectious Diseases.

He and his Baylor coworkers recently launched a prospective trial to test their hypothesis that some identifiable aspect of vaginal colonization with *U. urealyticum*—one candidate is *Ureaplasma* biovar type—will correlate with placental colonization. If that indeed turns out to be the case, the next step will be a treatment study aimed at clearing placental infection in order to reduce the rate of preterm birth.

The best drug for use in this setting remains unclear. Erythromycin has often been used in trials aimed at eradicating vaginal infection; however, resistance of *U. urealyticum* to this antibiotic is a growing problem.

Tetracyclines show the best efficacy in vitro but are inappropriate for use in pregnancy. One of the quinolones may turn out to be the best choice, Dr. Weisman said. ■

Placental Colonization/Infection Rates and Perinatal Outcome

	Gestational Age at Delivery (wk)	Prevalence of Placental Colonization: *U. urealyticum*	Prevalence of Placental Colonization: Group B Streptococcus
Preterm birth group (n = 58)	26.4	41.4%	15.5%
Complicated controls (n = 27)	39.2	40.8%	4.2%
Uncomplicated controls (n = 167)	38.8	14.8%	13.1%

Source: Dr. Weisman