Urinary PlGF Predicts Early-Onset Preeclampsia

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Vienna — Decreased urinary placental growth factor at midgestation is strongly associated with the subsequent development of early-onset preeclampsia, S. Ananth Karumanchi, M.D., reported.

"Low urinary PlGF antedates the clinical diagnosis of preeclampsia and may serve as a screening test to predict who will develop early-onset disease," Dr. Karumanchi said at the 14th World Congress of the International Society for the Study of Hypertension in Pregnancy.

The findings, published soon after the congress, come from a nested case-control study within the Calcium for Preeclampsia Prevention trial of healthy nulliparous women enrolled at five U.S. university medical centers during 1992-95. Frozen serum and urine samples from 120 women with preeclampsia were compared with those of 120 matched normotensive controls (JAMA 2005;293:77-85).

In all the women, urinary PlGF levels increased during the first two trimesters, with a more rapid increase after 21-24 weeks and a peak at 29-33 weeks. However, those levels were significantly lower among the women who subsequently developed preeclampsia at weeks 25-28, 29-32, and 33-36. Differences were particularly large between the controls and the women who subsequently developed preeclampsia before 37 weeks or who had preeclampsia with a small-for-gestational age (SGA) infant.

Alterations in urinary PlGF levels at 21-32 weeks were also more pronounced in women who subsequently developed preeclampsia before 37 weeks (87 pg/mL) than among those who had onset of preeclampsia at term (223 pg/mL).

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At 33-42 weeks, those levels were 22 vs. 118 pg/mL, lead author Richard J. Levine, M.D., of the National Institute of Child Health and Human Development, Bethesda, Md., and his associates reported in the published article.

The women were divided by quartiles of urinary PlGF obtained at 21-32 weeks' gestation and the results adjusted for gestational age at specimen collection, storage time, body mass index, and maternal age.

Compared with women in the upper three quartiles, the odds ratio was 22.5 for later development of preterm preeclampsia among the women with PlGF concentrations in the lowest quartile (less than 118 pg/mL).

The association was even stronger when restricted to just morning urine specimens, with an odds ratio of 39.5.

For term preeclampsia, the adjusted odds ratios of lowest vs. the upper three quartiles of PlGF concentration were 2.2 at 21-32 weeks and 2.3 at 33-42 weeks' gestation.

The data also suggested a strong association between low urinary PlGF and a substantially increased risk for preeclampsia with an SGA infant, but the numbers were too small to make a stable estimate, Dr. Levine and his associates noted.

Adjusting the results for urinary creatinine concentration did not change the strength of the associations, they said.

Previous data from this research group showed that increased circulating serum levels of the angiogenic factor soluble fms-like tyrosine kinase (sFlt-1) were predictive of subsequent preeclampsia (N. Engl. J. Med. 2004;350:672-83).

But because the sFlt-1 molecule is too large to be filtered into urine, the current study focused on PlGF, which binds to sFlt-1, as a more clinically feasible alternative. If a reliable dipstick assay could be developed for urine screening of all pregnant women for urine PlGF, then subsequent serum measurements of both PlGF and sFlt-1 could minimize false-positive results from urine testing, the investigators suggested.

At the congress, Dr. Karumanchi, a nephrologist at Beth Israel Deaconess Medical Center, Boston, said, "Obviously, this is a retrospective study done using specimens frozen for several years, and we don't know if it can be reproduced prospectively. Nevertheless, it does prove the hypothesis that angiogenic factors play a critical role in the pathogenesis of this syndrome." ■

No Cognitive Deficits Seen During Magnesium Tx for Preeclampsia

Vienna — Preeclamptic women on magnesium sulfate treatment do not appear to be at increased risk for cognitive deficits, Judith Hibbard, M.D., reported at the 14th World Congress of the International Society for the Study of Hypertension in Pregnancy.

In fact, women being treated in that manner appear to have better attention and working memory capacity than do normotensive laboring women, said Dr. Hibbard, professor of ob.gyn. at the University of Illinois at Chicago, who presented the paper for Sarosh Rana, M.D., of the University of Chicago.

These preliminary findings come from a study that was prompted by a news report of a nanny from Mexico who delivered and abandoned her baby on a Florida beach. She was arrested, but all charges were dropped when the physician at a local hospital stated that the mother had preeclampsia, and that associated mental changes could have prompted her temporary irrational behavior.

An initial literature search yielded a small amount of data suggesting that mild cognitive deficits may occur during normal pregnancy, as well as a few anecdotal reports of psychosis, but no previous formal studies looking specifically at cognition in preeclampsia.

Thus, the current study was initiated in which a battery of neurocognitive tests were administered twice to three groups of women: 15 with preeclampsia who were treated with $MgSO_4$, 15 women in preterm labor who received tocolytic $MgSO_4$, and 15 normal laboring women. Tests assessing intelligence (IQ), auditory comprehension, attention, memory, pain, and distress were first performed prior to delivery (at least 2 hours after initiation of $MgSO_4$ in the preeclamptic and preterm groups and shortly after admission in the controls), and again after delivery (at least 12 hours after discontinuation of $MgSO_4$ in the two treatment groups).

Prior to delivery, there were no apparent differences in age, parity, IQ, education, auditory comprehension, or fatigue level among the three groups. Distress was greater among the preeclamptics, whereas pain was higher in the normal controls, Dr. Hibbard noted.

Immediate verbal memory was similar before and after delivery within the three groups. However, delayed verbal memory improved in all three of the groups following delivery, and significantly so in the preeclamptics and preterm patients.

Digit span scores, which assess attention, did not differ before and after delivery in any group, but were significantly better at both time points in the preeclamptic patients on $MgSO_4$ than they were in the other two groups: Out of a possible 30, the preeclamptics scored 18.8 post delivery, compared with 16.86 among the normal laboring women and 14.8 among the preterm patients.

Similarly, whereas all three groups improved modestly post delivery on letter-number sequencing, which assesses attention and working memory, the preeclamptics also did better at both end points than did the other two groups.

Magnesium has been shown to have neuroprotective actions in cerebral ischemia and is a cerebral vasodilator for the ischemic—but not for the normally perfused—brain. This difference might explain the adverse cognitive effects of $MgSO_4$ on women in preterm labor and the absence of those effects in the preeclamptics, Dr. Hibbard said.

These results are part of a larger study that is looking at cognition among women with preeclampsia prior to the administration of magnesium, as well as among nonpregnant women, she said. ■

Exposure to $MgSO_4$ Appears Not to Raise Offspring's Risk

Vienna — The use of magnesium sulfate for the treatment of preeclampsia does not appear to increase the long-term risk of death or neurosensory disability in children, Lelia Duley, M.D., reported at the 14th World Congress of the International Society for the Study of Hypertension in Pregnancy.

The findings come from a follow-up study of subjects who participated in the landmark multinational Magpie (Magnesium Sulfate for Prevention of Eclampsia) Trial, in which 10,141 pregnant women with preeclampsia—from the developed and the developing world—were randomized to receive magnesium sulfate ($MgSO_4$) or placebo. Women who received $MgSO_4$ had a 58% lower risk of eclampsia and a 45% lower risk of death, with no clear difference in the risk of death among the newborns up until the time of hospital discharge (Lancet 2002;359:1877-90).

Now, an 18-month follow-up among 4,782 women and 4,483 children from the original trial suggests that in utero exposure to the drug is not associated with long-lasting damage. "It's very reassuring," said Dr. Duley an obstetric epidemiologist at the Resource Center for Randomized Trials, Institute of Health Sciences, Oxford, England.

A total of 13.9% of the children of the mothers who received $MgSO_4$ before delivery had died by the time of follow-up, not significantly different from the 12.7% in the placebo group. Approximately half from each group were stillborn, said Dr. Duley, who served as principal investigator for both parts of the trial.

Among the survivors, 1,283 children from the $MgSO_4$ group and 1,327 whose mothers received placebo were screened using the Ages and Stages questionnaire, which assesses neurosensory function. A total of 311 $MgSO_4$ and 325 placebo children scored positively. Of those, further assessment was conducted in 217 $MgSO_4$ and 215 placebo subjects.

Neurosensory disability was found in 19 $MgSO_4$ and 27 placebo children, including blindness in 3 from each group, deafness in 3 $MgSO_4$ and 1 placebo subject, and cerebral palsy in 3 $MgSO_4$ and 9 placebo children.

In all, death or disability occurred in 15% of the $MgSO_4$ and 14.1% of the placebo children. None of the differences were statistically significant, Dr. Duley said.

Among the mothers, there were no significant differences in deaths before or after discharge or in serious morbidity potentially related to the preeclampsia, she reported. ■

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