Study casts doubt on plans to scale up preterm birth treatment in low resource settings

October 16 2014, by Robert Bock

A study by a National Institutes of Health research network calls into question plans to increase access to steroid treatment for pregnant women in low resource settings at high risk for preterm birth. The study concluded that the treatment—a standard, life-saving practice in high income countries such as the United States—could potentially cause harm in low resource settings where many births take place outside the advance care hospitals that are standard in high income countries.

The researchers are uncertain as to why the therapy did not offer the clear benefit in the low income countries that it provides to preterm infants in high income countries. Potential reasons range from some unknown aspects of the intervention itself—the methods the researchers devised to teach local birth attendants how to administer the drug outside hospital settings—to the possibility that, despite enhanced lung function, preterm infants may simply be in greater need of the advanced hospital care common in high income countries.

The steroid therapy works by triggering the lungs of a preterm infant to mature so that he or she can absorb oxygen. The treatment has been proven to increase the survival rate of preterm infants in high and middle income countries. Steroid treatment is routinely prescribed to women at risk of giving birth before the 34th week of pregnancy in the United States and in other high income countries. Because of its proven effectiveness in the high income countries, health care workers have

begun efforts to increase access to women in low resource settings in low and middle income countries. Many health experts have called for increasing access to the drug so that it is routinely provided in underdeveloped countries as well. The study was undertaken as a test to determine the feasibility of providing the treatment in low resource settings.

For the study they conducted in low resource settings, the researchers devised an intervention to teach local birth attendants how to identify women who might benefit and to provide the drug to women who frequently deliver without the advanced hospital care facilities that are common in higher income countries.

The study enrolled women considered at risk for preterm birth, in several countries in Africa, Asia and Central and South America.

Compared to a control group, there was no difference in survival rates among infants considered to have been born preterm, regardless of whether or not their mothers took part in the intervention, the study found. Moreover, combined death rates for infants born to all of the women in the intervention group were slightly higher, as was the mothers' rate of post-birth infection.

"Many public health experts had believed steroid therapy before birth would save as many lives in low resource settings as it does in high income countries," said study author Marion Koso-Thomas, M.D., M.P.H., pediatrician and medical officer in the Pregnancy and Perinatology Branch at NICHD. "These results are extremely disheartening, but they underscore the critical importance of studying even an established treatment before introducing it to a new setting."

The study, appearing online in *The Lancet*, was conducted by researchers in the Global Network for Women's and Children's Health Research at

the NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

Additional support for the study was provided by the World Health Organization.

For the intervention, community health workers were taught to recognize the signs and symptoms of impending preterm birth. The workers were provided with measuring devices to help them estimate gestational age and boxed kits containing the drug and all the supplies needed to administer it. They were also instructed to inform women at risk of preterm birth that they should deliver in a hospital or higher-level care facility if at all possible.

The researchers were unable to determine why the intervention did not improve survival rates among the infants in the study, Dr. Koso-Thomas explained. Similarly, they could not determine whether it was the drug itself that led to the higher death rate, or some other aspect of the intervention.

"Our results do not support offering this therapy to women in low resource settings who do not have access to hospital care," Dr. Koso-Thomas said.

The study's first author was Fernando Althabe, M.D., of the Institute for Clinical Effectiveness and Health Policy in Buenos Aires, Argentina. The effort also involved researchers from several institutions in the United States and abroad. The 18 month study enrolled more than 100,000 pregnant women in Argentina, Guatemala, India, Pakistan, Kenya, and Zambia.

The authors noted that a large number of studies conducted in the United States and other high income countries have shown that giving

corticosteroids, like dexamethasone, to women at high risk for delivering prematurely is one of the most effective means for reducing newborn deaths associated with preterm birth. The treatment causes the fetus' lungs to mature, thereby reducing the chances for respiratory problems that would otherwise occur in a preterm infant's underdeveloped lungs. The authors added that although other studies had also shown similar benefit for steroid use in higher resource settings in middle-income countries like Brazil and South Africa, no studies had been undertaken in low resource settings. Moreover, all of the previous studies had been undertaken in hospitals with newborn intensive care units and the capacity to provide support for respiratory problems in the infant.

Dr. Althabe said that, because of the success of steroid therapy in high-income countries, many public health experts have been interested in extending the therapy to low income countries.

According to the study authors, 80 percent of women at high risk for preterm delivery in high-income countries receive steroid therapy, in contrast to 10 percent in low-income countries. Also, less than half of births in low-income countries occur in hospitals in which steroid therapy is available. In many low-income countries, health care providers lack ultrasound equipment and other means to assess accurately a woman's gestational age, an important prerequisite for steroid therapy. In addition, many women in these countries don't keep track of the date of their last menstrual period, which further compounds the difficulty in estimating gestational age. In low-income settings, many birth attendants lack the training to administer steroid therapy, and health care facilities may not have supplies of steroids on hand.

In the study, women were given the steroid treatment only if they had signs and symptoms that indicated a high risk of delivering before the 36th week of pregnancy. For cases in which the date of the last menstrual period was not known, health care workers were provided

with a specialized tape measure to record the height of the uterus—an indication of gestational age.

The intervention was provided in specified geographic areas. Women were assigned at random to either the steroid intervention group or to receive standard care only (the control group). Because it was difficult, in many cases, to obtain a precise estimate of gestational age at birth, the researchers considered an infant to have been born preterm if he or she had a birth weight lower than the 5th percentile, among all the infants born in a study location. Although some term infants are born at low birth weight, most infants who are born at low birth weight are preterm.

Of the more than 47,000 births to women in the intervention group, 5.2 percent were below the fifth percentile. Of the more than 50,000 births in the standard care group, 4.3 percent were below the fifth percentile. In the intervention group, 45.2 percent of the women delivering infants below the fifth percentile had been given steroids. For the standard care group, 10.4 percent who gave birth to infants below the fifth percentile had received steroids. The women in the standard care group, Dr. Koso-Thomas explained, did not receive steroids as part of the study, but may have received the treatment from local health care workers as part of the local standard of care.

For all the infants below the fifth percentile, newborn deaths by the 28th day of life did not differ significantly between the intervention group and the control group: 225 per thousand, compared to 232 per thousand. However, among all the infants in the study, more deaths at 28 days occurred among the intervention group than the control group: 27.4 versus 23.9 per thousand. Similarly, perinatal mortality—stillbirths and infant deaths in the first week of life—were also higher for the intervention group: 48 versus 42.9 per thousand.

For mothers in this study, the rate of post-birth infections was higher in

the intervention group (2.5 percent) compared to the control group (1.7 percent.)

Based on their results, the study authors recommended that, given that previous studies have proven that the steroid therapy is beneficial in advance care hospital settings, efforts to increase use of steroid therapy in low resource areas should be limited to women who are able to give birth in hospital settings.

The study authors added that the findings do not apply to how prenatal steroids are administered in advanced care hospital settings, in which they have been demonstrated to save the lives of preterm infants.

Provided by National Institutes of Health