


Reply

To the Editors:

I appreciate Dr. Goodlin's interest in my overview. I share his concerns for the high rates of neonatal morbidity and mortality associated with congenital sepsis.

In our retrospective study to which Dr. Goodlin refers, the mortality with proved congenital sepsis was 50%. Congenital sepsis often was associated with premature rupture of the membranes (PROM) and always was associated with maternal infectious morbidity. Routine antenatal administration of antibiotics to our patients with preterm PROM at that time may explain the low incidence of neonatal sepsis caused by group B streptococci. The most commonly isolated organism was Escherichia coli, perhaps as a result of the antenatal treatment with penicillin-erythromycin. It should be noted that internationally group B streptococci are not considered to be the most common cause of neonatal sepsis; gram-negative organisms predominate. Any prospective study designed to look at interventions to prevent neonatal infection with group B streptococci should include congenital sepsis caused by any organism as an outcome.

In our own unit, infection is the major cause of possibly preventable deaths beyond 28 weeks' gestation. The important role played by infection in perinatal morbidity and mortality and the difficulties experienced by perinatologists to prevent, diagnose, and treat fetal-neonatal infection associated with preterm PROM were indeed the very raisons d'être for my meta-analysis. The possible increase in neonatal infectious morbidity with antenatal steroid treatment was the reason for including in the overview only trials that reported the incidence of both respiratory distress syndrome (RDS) and neonatal infections.

If only two studies are compared, as in Goodlin's case with the studies by Cox et al. and Lubchenco et al., the difference in study results is the same whether the vantage point is Dallas or Denver. The decision as to which studies to include in an overview and the assessment of their quality must be based on preset criteria to avoid bias, as I stated in my article. The differences seen in the quality "scores" of certain studies probably can be explained by the different methods used by Dr. Goodlin and myself. Randomized controlled trials generally are viewed by physicians as the most useful source of data regarding clinical management because this study design controls for bias. The quality of randomized controlled trials varies, as does the quality of case reports, case-control studies, and cohort studies.

Williamson et al. have reviewed the quality of medical literature. They report on the correlation between the frequency of positive study findings and the adequacy of the methods used to obtain these results; this rate was 80% in 449 inadequately designed studies and 25% in 305 adequately designed studies.

In my overview statements made by authors regarding statistical significance for entry characteristics and outcomes were not taken for granted to be correct. Information reported in the trials was subjected independently from the authors' findings to statistical analysis. This occasionally resulted in a different p value than reported by the authors.

The study by Morales et al. does stand out as different from the four other accepted studies on antenatal treatment with steroids to prevent RDS. The treatment effect in the study by Morales et al. was at least twice that of the treatment effect noted in any of the other studies. In the study by Morales et al., the mean birth weight was statistically higher in the treatment group than in the control group (p = 0.003).

Morales et al. noted that antenatal dexamethasone administration was particularly effective in protecting nonwhite babies against RDS (44% vs 16%). The reduction in the white population was much less (55% vs 35%) and was similar to that seen in the other four studies. In the study by Morales et al., there was a statistically significantly larger number of nonwhite women in the treatment group (p = 0.01). Morales et al. enrolled 250 patients with singleton pregnancies, but the outcome was reported for only 245 neonates. The randomization process used in this study was by health record number, which is an imperfect method. Critics of the study, including Porreco and Burke from the Maternal-Fetal Medicine program in Denver also have noted a much lower incidence of RDS in the treatment group (26%) than in the control group (54%) after a treatment and latency period of <24 hours. Overall, it appears that the treatment group included patients that were at a lower risk of developing RDS...
than the control group. Because of these concerns, it was justified and necessary to report the findings of my meta-analysis with and without the study by Morales et al. If one adds the adverse outcomes (RDS plus infection) in the five accepted studies, there is a statistically significant benefit of antenatal steroids (treatment group 99/285, control group 127/277, $p = 0.01$). However, if the study by Morales et al. is excluded, the benefit disappears (treatment group 58/164, control group 53/153, $p = 0.99$). None of these four separate studies or my meta-analysis has the power (80%) to demonstrate a significant ($p < 0.05$) increase in neonatal infection with steroid treatment. Such a study would require a sample size of 950 to 1000 patients. It also should be noted that the diangosis of RDS and congenital infection does not carry the same weight regarding outcome, the mortality being seven times higher in congenital infection (Hannah M. Ohlsson A. Unpublished data). The meta-analysis does, however, confirm a significant increase in endometritis ($p = 0.002$). Contrary to what Dr. Goodlin states, Morales et al. did not report on the incidence of endometritis.

Whether appropriate treatment with antibiotics in comparison to antenatal steroids can eliminate the increased risk for maternal infection and the possible increased risk for fetal-neonatal infection, resulting in a better overall maternal-fetal-neonatal outcome, still is not known. This appears, however, to be a very important question for obstetric and neonatal perinatologists to answer in cooperation, as soon as possible, in a multicenter randomized controlled trial. It is time to replace strong beliefs expressed by perinatologists (obstetric and neonatal) with validated facts. Instead of quoting Lewis Carroll, I prefer to cite his countrymen, Chalmers et al.: "If perinatal medicine is to shed the reputation it has gained in some quarters for reckless development of clinical practice ungrounded in good evidence, then not only must we try harder to ensure that patients are involved in well-controlled rather than poorly controlled experiments, we must also make more determined efforts to ensure that the quality of these controlled experiments improves."

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REFERENCES

Cervical length may change during ultrasonographic examination
To the Editors:
Abdominal and vaginal ultrasonography has been shown to hold some promise in the evaluation of the gravid cervix uteri. It has been used not only for measurement of the cervical length, but also for evaluation of the shape of the internal cervical os and canal. The significance of "funneling" of the in-