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Corticosteroids for fetuses with congenital diaphragmatic hernia: can we show benefit?☆

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Abstract

Background and Purpose: Prenatal corticosteroids have been used in fetuses with congenital diaphragmatic hernia (CDH). We tested the utility of steroids by 2 methods.

Methods: Mothers carrying fetuses with CDH were randomized to 3 weekly doses of betamethasone or placebo starting at 34 weeks. Patients were followed until death or discharge. In a separate cohort study, the CDH Registry was used to compare infants who received prenatal steroids to those who had not.

Results: Thirty-four patients were enrolled at 7 centers, with 32 completing the trial. There were 15 placebo and 17 steroid patients. There was no difference in survival, length of stay, duration of ventilation, or oxygen use at 30 days. For the cohort study, we looked at infants older than 34 weeks who were born after October 2000 when data on prenatal steroids were collected. There were 1093 patients; 390 were evaluable, with 56 receiving steroids. There was no difference in survival, length of stay, ventilator days, or oxygen use at 30 days.

Conclusion: Neither the trial nor the CDH Registry suggest that late prenatal corticosteroids benefit fetuses with CDH. More than 1700 mothers and fetuses would need to be enrolled in a trial to

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show a 10% improvement in survival. It is unlikely that late steroids offer benefit to most fetuses with CDH.

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in every 2000 to 4000 deliveries [1,2]. The overall mortality for fetuses with isolated potentially correctable CDH diagnosed before 24 weeks of gestation is approximately 58% [3]. Despite many advances in neonatal care, mortality remains high. In addition to the high mortality, CDH ranks among the most costly of correctable conditions, with an estimated cost per new case of $250,000 and an overall estimated yearly cost of $264,000,000 in the United States [4].

With the widespread use of prenatal ultrasound to establish appropriate gestational age and evaluate fetal anomalies, an increasing proportion of infants with CDH are diagnosed before delivery. The ability to diagnose CDH in utero has allowed the development of surgical approaches to these fetuses, which has been recently reviewed [5-7].

The underlying pathophysiology in such infants appears to be a combination of lung hypoplasia and persistent pulmonary hypertension. It has been suggested that the lungs of infants with CDH resemble those of premature infants with surfactant deficient lung disease. George et al [8] carefully assessed the lungs of 10 infants who died of CDH and found evidence of not only lung hypoplasia, but also lung immaturity. The lungs of infants with CDH demonstrate structural distortion of bronchi with airspaces lined with cuboidal epithelium, delayed acinar development, and hyaline membranes. In the nitrofen rat model of CDH, there is evidence that antenatal steroids reverse many of the histological and biochemical indexes of immaturity [9,10].

Given the experimental data, a number of centers have established protocols for the routine use of prenatal corticosteroids for fetuses with CDH [11]. One series of only 3 patients purported benefit from multiple doses of corticosteroids for fetuses with CDH [12]. The use of corticosteroids for CDH has been adopted in the absence of any controlled study in human subjects.

In view of the previously described observations and lack of controlled data, we began a prospective, multicenter, double-blind, placebo-controlled randomized clinical trial to evaluate the effect of maternally administered steroids to fetuses with diagnosed CDH. We also evaluated data from the CDH Study Group registry comparing infants with CDH who had received prenatal corticosteroids to those who had not.

The primary hypothesis was that the administration of antenatal corticosteroids after 34 weeks of gestation to women with fetuses with proven CDH will significantly reduce the mortality for such fetuses compared with untreated fetuses.

1. Material and methods

For the randomized trial, mothers carrying fetuses with CDH were identified with a prenatal ultrasound before 34 weeks of gestation. The mothers were approached for written informed consent, and at 34 weeks of gestation, the patients were randomized to receive either steroids or placebo by a central randomization center. Mothers received either betamethasone (12.5 mg) or placebo every 24 hours for 2 doses and then once a week for 2 more weeks (Fig. 1). The drugs were administered by a research nurse; all investigators were blinded to treatment group.

Data collected before delivery included maternal demographics and fetal ultrasound information. Postnatal data collection was the same as for the CDH Registry and included demographic data, apgar scores, diaphragmatic defect size, presence of anomalies, treatment details, and outcome. After delivery, infants were managed in their respective institution with local standard care. Outcome variables include mortality, ventilator days, need for oxygen at 30 days after delivery, and length of hospital stay. An independent data safety monitoring committee evaluated the study results.

We also evaluated the impact of steroid use in prospective cohort study using data from the CDH Study Group Registry. The CDH Study Group is a voluntary collaboration of tertiary referral centers that provide care for CDH patients. All live born infants with CDH who are born at or transferred to a participating center are entered into the database. Data have been collected prospectively until death or discharge from the hospital on all live born patients with CDH starting in 1995. For this study, we used data from patients born between October 2000 and March 2005 from

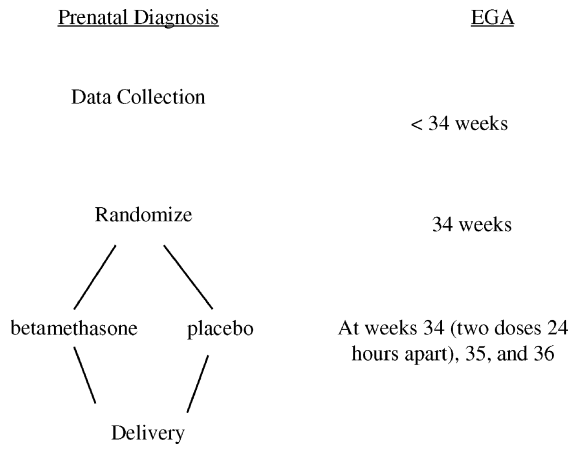

Fig. 1 Flow diagram of the randomized trial study design.