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ORIGINAL ARTICLE

W. D. A. Ford · C. P. Kirby · C. S. Wilkinson
M. E. Furness · A. J. Slater

Antenatal betamethasone and favourable outcomes in fetuses with 'poor prognosis' diaphragmatic hernia

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Abstract Congenital diaphragmatic hernia (CDH) is a common abnormality affecting 1 in 2,000 gestations. The mortality exceeds 50% despite recent advances in postnatal treatment. The widespread antenatal use of glucocorticoids to induce lung maturation in fetuses at risk of premature delivery suggests a potential for a therapeutic effect in other fetuses with impaired lung development. The parents of three fetuses referred with CDH and features suggesting a poor postnatal prognosis (early diagnosis, liver herniation, and lung area-to-head circumference ratio < 1.0, or associated abnormalities) elected to receive maternal betamethasone starting at 24 to 26 weeks' gestation rather than undergo a fetal tracheal plug. All three infants survived and were extubated within 10 days. The long-term use of antenatal steroids in the treatment of CDH may thus be of benefit and warrants further study.

Keywords Fetal diaphragmatic hernia· Steroids

W. D. A. Ford · C. P. Kirby
Department of Paediatric Surgery,
Women's and Children's Hospital,
Adelaide, Australia

C. S. Wilkinson
Department of Perinatal Medicine,
Women's and Children's Hospital,
Adelaide, Australia

M. E. Furness
Department of Women's Ultrasound,
Women's and Children's Hospital,
Adelaide, Australia

A. J. Slater
Department of Paediatric Intensive Care,
Women's and Children's Hospital,
Adelaide, Australia

W. D. A. Ford (✉)
Department of Paediatric Surgery,
Women's and Children's Hospital,
72 King William Road,
North Adelaide SA 5006, Australia

Introduction

Newborns with congenital diaphragmatic hernia (CDH) have small and immature lungs [16]. Theoretically, to achieve maximal survival both factors should be corrected, but to improve only one could improve survival significantly. Steroids may be able to improve lung maturation and hence postnatal lung function. They have been shown to improve lung function in premature lambs without a CDH [15] and full-term lambs with a CDH by increasing lung compliance [19], improving morphogenesis [7], accelerating surfactant synthesis [20], and decreasing pulmonary-vascular wall thickening [13, 21]. As betamethasone (BMS) has had widespread clinical use to reduce the incidence of hyaline membrane disease [2, 10], it would appear to be the appropriate first choice. Therefore, we opted to treat fetuses with CDH with repeated doses of BMS administered maternally to determine if there was any suggestion of improved lung function after birth. As repeated doses of steroids have also been shown to have a deleterious effect on the lamb fetus [8, 9, 17], rather than treat all fetuses with a prenatal diagnosis of CDH we opted to try to treat only those with a "poor prognosis".

Materials and methods

Three antenatally-diagnosed fetuses with a poor-prognosis CDH (two with a low lung area-to-head circumference ratio [LHR] and one with another significant structural abnormality) were treated with repeat doses of antenatal steroids in the period 1997–2000. The fetuses represent three consecutive patients with poor prognosis who presented to the antenatal diagnosis and counselling group, Women's and Children's Hospital, over a 4-year period. Fetuses who did not appear to have a poor prognosis were not offered this therapy.

Case reports

Case 1 A left-sided CDH was diagnosed by routine ultrasound (US) in a male fetus at 18 weeks' gestation. At 23 weeks' gestation the LHR was 0.9, and part of the liver appeared intrathoracic. A LHR below 1.0 is associated with a poor prognosis and a high risk

of mortality, 100% in two small series [6, 12], especially where the liver is in the chest. After initial enthusiasm for fetal surgery using a tracheal occlusion technique, the parents declined fetal intervention following explanation of the obstetric risks, but accepted the risks associated with the use of repeat doses of antenatal BMS.

Maternal administration of BMS was commenced at 26 weeks' gestation: an initial deep IM injection of 11.4 mg followed by injection of 11.4 mg 24 h later and subsequent doses of 11.4 mg on alternate weeks until delivery was induced at 38 weeks. At birth, the infant required modest ventilation (peak inspiratory pressure/positive end-expiratory pressure [PIP/PEEP] 18/3; mean airway pressure [MAP] 9 cm H_2O; rate [R] 30 min, inspiratory time [T_i] 0.6 s inspired oxygen fraction; [$Fi0_2$] 0.85). Blood gases at 6 h of age on these settings demonstrated: pH 7.41, $PaCO_2$ 33 mmHg, and PaO_2 233 mm Hg. Pre- and post-ductal O_2 saturations were equal and echocardiography demonstrated left-to-right ductal flow prior to operation at 24 h. The left lobe of the liver, gut, and spleen were reduced from the thorax prior to primary diaphragmatic repair. The infant was extubated at 10 days of age and discharged home on day 18.

Formal assessment of development and sight at 2 years of age detected no abnormality, and the child is about to begin preschool at 4 years of age.

Case 2 A left CDH was identified on antenatal US at 22 weeks' gestation. The LHR was 1.0. BMS was commenced at 24 weeks' gestation and continued fortnightly until 38 weeks using the same regimen as in case 1. The 18-year-old mother developed gestational diabetes requiring insulin, which may have resulted from the glucocorticoid therapy. The infant was delivered at 39 weeks, electively intubated, and mechanically ventilated. At 4 h of age the ventilator settings were: PIP/PEEP 20/3; MAP 10 cm H_2O; R 45; T_i 0.5 s; $Fi0_2$ 0.3. Blood gases showed: pH 7.29, $PaCO_2$ 38 mmHg, and PaO_2 70 mmHg. The hernia was repaired on day 2 of life, and the infant was extubated 5 days later. Growth and development have been normal up to 12 months of age.

Case 3 Antenatal US at 20 weeks' gestation demonstrated a small CDH with no obvious mediastinal displacement. Within 2 weeks, however, there was a marked increase in volume of the hernia with lung displacement. At the same time a large ventricular septal defect (VSD) was visualised. The hernia volume increased further so that by 21.5 weeks' gestation the LHR was 1.5, which on its own indicated a good prognosis. Because of the associated cardiac defect, a decision was made to offer the patient the same regime as above starting at 26 weeks' gestation. The fetus was delivered at term and was easily ventilated (PIP/PEEP 20/4; MAP 11 cm H_2O; R 55; T_i 0.5 s; $Fi0_2$ 0.65). Blood gases at 5 h of age demonstrated: pH 7.29, $PaCO_2$ 45 mmHg, and PaO_2 68 mmHg. The infant was found to have multiple congenital anomalies with features of the VATER association with a CDH. These included complex congenital heart disease (atrial septal defect, VSD, hypoplastic mitral valve, and hypoplastic left ventricle), an anterior ectopic anus, and bilateral thumb anomalies in addition to the CDH. The infant underwent surgical repair of the CDH on day 2 of life and was extubated 5 days later. At 6 months of age he is surviving despite the severe cardiac defects and has undergone cardiac surgery. Pulmonary function is, however, near normal without respiratory distress. A review of the LHR after delivery showed it to be well over 1.0. The patient is included to show that survival occurred despite the cardiac failure.

During the same period of time three other babies were born without an antenatal diagnosis of CDH; two of these died. In addition, another five fetuses underwent termination of pregnancy at parental request.

Discussion

All of the mothers and their partners were counselled that the antenatal use of steroids in the treatment of CDH is an untried aspect of a well-established therapy, that our antenatal use of steroids was usually limited to a single course of two injections given only if the baby was considered at risk of being born before 34 weeks' gestation. This new form of treatment for CDH, might have both beneficial and deleterious effects on the fetus, particularly because of the repeat-dose administration. The discussion included the known advantages of steroid therapy: reduced respiratory distress syndrome, reduced intraventricular haemorrhage, and reduced necrotising enterocolitis, should the baby be born prematurely [2]. Recent concerns regarding growth restriction [9] and evidence of delays in nerve myelination in animal studies when steroid therapy was repeated [8, 17] formed part of the discussion, as did the poor prognosis of the CDH.

Attempts at determining which fetuses with CDH have a poor prognosis have been made over the last 2 decades, with improving results [6, 11, 12]. Those that have some degree of reliability include early diagnosis (before 25 weeks' gestation), the presence of liver in the chest, and a low LHR [6]. A recent survival analysis demonstrated no patient surviving with an LHR below 1.0 ($n = 3$) despite ECMO support [11], or in another report where the LHR was less than 0.6 ($n = 5$) [12].

Infants with CDH have small, morphologically immature lungs with pulmonary-vascular wall thickening (PAWT) and surfactant deficiency [16]. Antenatal steroid therapy in experimentally-induced CDH has led to accelerated surfactant synthesis and release [20], increased lung compliance [19], improved morphogenesis [7], and prevention of PAWT [13, 21]. Antenatal steroid therapy has similarly been shown to suppress pulmonary endothelial angiotensin-converting enzyme activity to levels equivalent to those seen in normal lungs, potentially reducing the predisposition to pulmonary hypertension [14].

Animal studies suggest that the improved pulmonary vascular resistance at birth following steroid administration is mediated by increased nitric oxide synthase activity, but that the timing and duration of steroid administration appear to be critical to this response [5]. Animal studies have also shown that prolonged antenatal steroid administration delays myelination and growth of fetal brain areas, particularly the hippocampus [4, 22], but the number and function of oligodendrocytes appears to return to normal postnatally [1]. Clinical trials of maternally-administered corticosteroid show no evidence of increased disability, but numbers are small [2, 3].

In the three CDH infants presented, prolonged steroid administration over 10 weeks of pregnancy may have contributed to the ease of ventilation, absence of pulmonary hypertension, and survival. Further reports of prolonged steroid use in CDH will be required to determine the efficacy of this therapy in humans, but this treatment, if proven successful, may obviate the need for antenatal surgical intervention and reduce the need for expensive technology to support the baby after birth.

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Author's note An article published since this paper was submitted [Sbragia L, Paek BW, Filly RA, Harrison MR, Farrell JA, Farmer DL, Albanese CT (2000) Congenital diaphragmatic hernia without herniation of the liver: does the lung-to-head ratio predict survival? J Ultrasound Med 19: 845–848, describes 20 fetuses with a CDH but without liver in the chest. There were 9 fetuses with LHR < 1.4 and 11 with LHR > 1.4. There was no difference in survival between the two groups. No fetus in this report had an LHR < 1.0. For those with LHR < 1.0 but not < 1.4 the outcome is presumably still poor, especially where there is also liver in the chest. But the study does cast doubt on relying on a LHR of < 1.0 as the only parameter of a poor prognosis.