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High-risk fetal congenital pulmonary airway malformations have a variable response to steroids

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Abstract

Background/Purpose: Anecdotal reports suggest that maternal steroids may arrest the growth of congenital pulmonary airway malformations (CPAMs), preventing or reversing hydrops. We reviewed our experience with CPAMs to determine the fetal response to steroid therapy.

Methods: This study is a retrospective review of all fetal CPAMs from 2004 to 2008. Fetuses with high-risk CPAMs that received at least one course of steroids were identified. Fetal magnetic resonance imaging and ultrasound data were used to classify the CPAMs, identify hydrops fetalis and follow the fetuses poststeroid dosing.

Results: Forty-four fetuses with CPAM were identified. Fifteen patients were found to have received at least one course of steroids. Thirteen were hydropic and 2 were nonhydropic. Seven of the 13 hydropic fetuses (54%) showed an initial response to steroid administration, whereas the 2 nonhydropic high-risk fetuses progressed to birth without developing hydrops. Seven of the 15 patients, however, resulted in fetal demise or early postnatal death, giving a survival rate of 53%.

Conclusions: High-risk CPAMs have a variable response to steroids. This variable response demonstrates the need for a placebo-controlled randomized study to more accurately determine the effect of steroids on hydrops and CPAM growth rates. Repeated steroid courses may not be helpful, and progression in CPAM volume to head circumference ratio (CVR) or hydrops should prompt open fetal surgery to prevent irreversible fetal insult.

1. Background/purpose

Congenital pulmonary airway malformation (CPAM) is a rare developmental abnormality of the lung characterized by a cystic mass of disordered pulmonary parenchyma with

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proliferation of terminal respiratory bronchioles and a lack of normal alveoli [1]. The natural history of these lesions follows a broad spectrum ranging from complete regression to rapid growth. This rapid growth may result in mediastinal shift, cardiac compression, hydrops fetalis, and polyhydramnios [2]. Without associated hydrops fetalis, the prognosis of prenatally diagnosed CPAM is generally favorable with good survival rates [3,4]. However, prenatally diagnosed CPAM associated with hydrops fetalis predicts a much higher mortality, approaching 100% without intervention [5]. As many as 33% of fetuses with CPAM will go on to develop hydrops and require fetal interventions [6,7]. In the setting of hydrops, these interventions have been shown to dramatically improve fetal survival [8].

The treatment of CPAMs with hydrops depends on whether the lesion is predominantly microcystic or macrocystic. Macrocystic CPAMs containing one or more dominant cysts can be treated by cyst aspiration and/or thoracoamniotic (TA) shunting, which often results in resolution of hydrops. In contrast, large microcystic CPAMs are more difficult to treat because they require open fetal surgery with resection to allow for resolution of hydrops.

Recently, Tsao et al [9] have suggested administering maternal betamethasone for treatment of CPAMs associated with hydrops fetalis. This treatment, in anecdotal experience, appears to result in resolution of hydrops and improved fetal survival. Peranteau et al [10] also demonstrated this finding in a small series of 11 patients with high-risk fetal CPAMs. To further evaluate this observation, we reviewed our experience in a quaternary referral center with high-risk fetal CPAMs treated with prenatal steroids.

2. Methods

From June 2004 to February 2008, the records of all patients referred to the Fetal Care Center of Cincinnati, Ohio, with the diagnosis of CPAM were reviewed after approval from the Institutional Review Board at Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (Institutional Review Board no. 07-08-19). Patients who had a diagnosis of high-risk fetal CPAM and who were treated with at least one maternal course of betamethasone (12.5 mg, intramuscularly ×2 doses) were further identified. High-risk fetal CPAM was defined as a CPAM associated with hydrops or a CPAM volume to head circumference ratio (CVR) greater than 1.6, which is predictive of developing hydrops in 75% of fetuses [7]. Hydrops was defined as an ultrasound-detected presence of abnormal fluid collections within at least one of the following locations: pleural, pericardial, or peritoneal cavities, skin, scalp, or placentomegaly.

The records of all the patients with high-risk CPAM were further reviewed, and the following data were recorded: location and size of lesion, type of lesion, that is, microcystic or macrocystic (one or more cysts >0.5 cm in diameter), gestational age at presentation, number of steroid courses, presence of hydrops at steroid dosing, time for hydrops resolution, surgical interventions (TA shunting, cyst aspiration, or salvage open fetal surgery), and outcome. Congenital pulmonary airway malformations were characterized using both ultrafast fetal magnetic resonance imaging and ultrasound techniques. Those fetuses that underwent resolution of hydrops after steroid administration were further classified as responders to steroid treatment.

3. Results

During the 44-month study period, 44 fetuses were referred to our institution with a prenatal diagnosis of CPAM. The mean CVR of all 44 fetuses at presentation was 1.51 ± 1.45 (range, 0.2-5.6). We identified 20 (45%) high-risk fetal CPAMs with a mean CVR of 2.62 ± 1.51. Of these 20 high-risk patients, 16 (80%) were hydropic with a mean CVR of 2.82 ± 1.63 and 4 (20%) were nonhydropic with a mean CVR of 1.82 ± 0.08. Thirteen of the 16 (81%) hydropic high-risk patients received steroids, and 2 of the 4 nonhydropic high-risk patients also received steroids. Of the 15 patients that received maternally dosed steroids, the mean gestational age at dosing was 24.0 ± 4.1 weeks (range, 18.9-31.7 weeks). There were no adverse effects caused by steroid administration either reported or recognized in these patients. The prenatal findings and outcomes are shown in Table 1.

The 2 nonhydropic patients (patients 1-2) with CVRs of 1.85 and 1.9 received one course of maternal betamethasone at 20 and 1/7 weeks' and 25 and 6/7 weeks' gestation, respectively. Both patients remained stable without developing hydrops, delivered uneventfully, and underwent successful postnatal CPAM resection. Currently, the children are alive and well.

Seven (54%) of 13 fetuses had evidence of hydrops resolution after steroid administration and were considered to be responders to steroid treatment (patients 3-9). However, of these 7 responders, 3 (43%) (patients 3-5) required additional therapeutic interventions (2 underwent TA shunting and one underwent salvage open fetal surgery). The 2 patients that required TA shunting had macrocystic lesions containing dominant cysts. After cyst decompression from TA shunting, hydrops resolved in these 2 fetuses after 6 and 63 days. The additional 4 responders (57%) (patients 6-9) had resolution of fetal hydrops with one course of steroids and did not require any further intervention. One of these fetuses (patient 7) had a profound reduction in CVR with resolution of the hydrops as illustrated in Fig. 1. Of these 7 fetuses that responded to steroids, 6 ultimately survived (patients 4-9). Although patient 3 had complete resolution of hydrops after salvage open fetal surgery, death occurred from unknown etiology 6 weeks postoperatively.

In the nonresponder group, there were no survivors. Patients 10 through 12 died with persistent hydrops despite