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Favorable outcomes in high-risk congenital pulmonary airway malformations treated with multiple courses of maternal betamethasone

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ABSTRACT

Background/purpose: Congenital pulmonary airway malformations (CPAMs) are rare congenital lung lesions often diagnosed by prenatal ultrasound. High-risk cases can result in hydrops and prenatal or postnatal demise. Antenatal betamethasone has resulted in improved survival but it is unclear how to manage patients who do not respond to a single course.

Methods: We present a bi-institutional retrospective review of patients treated with multiple courses of prenatal steroids for high-risk CPAMs between 2007 and 2013.

Results: Nine patients met inclusion criteria. All but one either had an increased CPAM volume ratio (CVR) or number of fluid-containing compartments involved after a single course of antenatal betamethasone, prompting additional courses. Four patients stabilized, three improved and two progressed after the second course. The two cases with disease progression underwent an in utero resection. There were one in utero fetal demise and two deaths within the delivery room. Both fetuses that underwent a fetal resection died. All but one mother who delivered a viable fetus had complications of pregnancy.

Conclusions: Multiple courses of antenatal betamethasone for high-risk fetal CPAMs often result in favorable short-term outcomes without the need for open fetal resection. Pregnancy complications are common and women within this cohort should be monitored closely.

Congenital pulmonary airway malformation (CPAM) is a developmental abnormality within the fetal lung resulting from terminal bronchial proliferation and abnormal alveolar development [1]. The natural course is variable as some lesions grow throughout gestation, while others enter a quiescent state and in some cases it has been suggested that they can completely resolve [2]. Previously, mortality resulting from CPAM with associated hydrops previously approached 100% [3–5] but has declined to 20–47% with the emergence of maternal betamethasone administration in the mid-second trimester [6–9].

CPAMs can be classified pathologically into several groups depending on cyst size, epithelial lining, and the presence or absence of a "solid" component [10]; however, characterization with imaging is more relevant for guiding fetal therapy and predicting prenatal outcomes. Macrocystic lesions, defined as one or more cysts greater than 5 mm in diameter on sonographic evaluation [11], often grow throughout pregnancy [12] and may contain dominant cysts that are amenable to aspiration and thoracoamniotic shunt placement. Alternatively, microcystic lesions, defined as cysts less than 5 mm in diameter [11], generally plateau or decrease in size after 26–28 gestational weeks [12]. They are more frequently associated with the development of nonimmune fetal hydrops and, for reasons unknown, are more responsive to prenatal betamethasone administration [13].

Antenatal betamethasone has become standard of care as the first-line therapy for fetuses with high-risk (CPAM volume ratio (CVR) $\geq$1.6 and/or hydrops) [7] microcystic or mixed lesions not containing a dominant cyst amenable to decompression. However, a subset of high-risk CPAMs does not adequately respond to a single course of steroids, leaving the fetus at risk for disease progression. Alternative treatment options include open fetal surgical resection or an additional course of steroids. There is currently little available information to guide the management of these pregnancies. In this report, we review treatment approaches and outcomes of fetuses who received multiple courses of maternal betamethasone at two tertiary fetal treatment centers.

1. Materials and methods

Following IRB approval, we performed a retrospective review of prospectively collected databases for all patients with a prenatal

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Table 1
Maternal and fetal characteristics.

Case	Maternal age	GA at presentation	CPAM location	CVR	Hydropic fluid
1	40	19	Left	3.7	Ascites
2	26	20	Right	2	Ascites, pleural effusion
3	36	21	Right	2.6	Ascites, scalp edema
4	40	19	Right	1.7	Ascites
5	36	30	Left	2.3	Ascites, pleural effusion
6	29	22	Left	2.8	Ascites, pleural effusion
7	25	19	Left	4.6	Ascites
8	29	26	Right	2.9	Ascites, scalp edema

GA, gestational age; CPAM, congenital pulmonary airway malformation; CVR, CPAM volume ratio.

diagnosis of CPAM evaluated at two North American fetal treatment centers (University of California, San Francisco or Cincinnati Children's Hospital Medical Center). Since antenatal betamethasone was initially implemented for the treatment of high-risk (CVR ≥ 1.6 and/or hydrops) CPAM in 2007, we included all cases of CPAMs treated between January 2007 and December 2013. Both institutions used the same criteria for steroid administration: high-risk CPAMs with a predominant microcystic component. Cases in which two or more courses of maternal betamethasone were administered for treatment of CPAM were identified. Each course consisted of once daily intramuscular administration of 12.5 mg of betamethasone to the mother for two consecutive days.

Details pertaining to prenatal course and imaging, as well as postnatal outcomes were recorded and evaluated. The CVR was calculated by dividing the CPAM volume (length × width × height × 0.52) by the head circumference [12]. Hydrops was defined as fluid within two or more compartments, including the thorax, abdomen, skin, and pericardium. Disease improvement, progression, or stabilization was defined as a decrease, increase or no change in the CVR or the number of fluid-containing compartments, respectively. Preterm delivery was prior to 37 weeks' gestation.

2. Results

A total of 276 fetuses with the diagnosis of CPAM were evaluated during the inclusion time period and 106 (38%) high-risk cases were identified. Of high-risk cases, 101 (95%) received maternal steroids. Eight (8%) received two or more courses of steroids and served as the focus of the subsequent analysis. Half of the CPAMs were right sided with a mean CVR on initial ultrasound of 2.8 (range 1.7–4.6, Table 1). All 8 cases were microcystic; however, 1 had a macrocystic component which was too small (largest cyst measuring 2.1 cm in greatest diameter) for thorocentesis or thoracoamniotic shunt placement (case #4). Hydrops was evident in 5 cases while 3 cases had fluid within only one compartment.

The mean gestational age (GA) at administration of the first course of antenatal betamethasone was 22 weeks (range, 19–30 weeks). Disease progression was seen in all but one case, prompting a second course of steroids, which was given at a mean GA of 25 weeks (range, 21–35 weeks). In case #5, the hydropic fluid resolved after the first course, but the CVR remained persistently elevated which led to administration of a second course. Ultrasonography following the second course demonstrated improvement in 3 cases, stabilization in 3 cases, and progression in 2 cases (Table 2).

Two fetuses progressed despite a second course of maternal betamethasone. Neither case had macrocystic elements and the CVR measurements were 4.6 and 2.9 (Table 1). In addition, each fetus exhibited signs of either cardiac decompensation or impending demise, prompting a fetal resection at 27 weeks' gestation. Both cases were complicated by postoperative oligohydramnios and in one case, the fetus had an episode of supraventricular tachycardia which spontaneously resolved on postoperative day one. A cesarean section was performed on postoperative day 4 owing to abdominal pain and fever, later diagnosed as chorioamnionitis on placental pathology. The newborn consequently expired from pulmonary hypoplasia at 80 minutes of life. In the other case, an ultrasound at 30 weeks' gestation demonstrated in utero fetal demise (IUFD).

Excluding the case resulting in an IUFD, six of the seven patients had a pregnancy complication which included mirror syndrome, preterm premature rupture of membranes, polyhydramnios, preterm labor (PTL), and chorioamnionitis (Table 3). The mean GA at delivery was 34 weeks (range, 28–39 weeks, Table 3), with 4 of the 7 fetuses born prematurely. Three were spontaneous preterm births and 2 were induced (one for mirror syndrome and another for chorioamnionitis). The high rate of prematurity and other pregnancy complications suggest that the hydropic state present in high-risk CPAM is a risk factor for complications of pregnancy.

Five of the 8 (63%) fetuses who received multiple courses of steroids survived. There was 1 IUFD and 2 perinatal deaths (Table 3). Of the 3 deaths, 1 fetus did not undergo prenatal resection (case #3). This fetus presented with a CVR of 2.6 and exhibited disease stabilization following the second course of steroids but delivered at 31 weeks gestation, and died from pulmonary hypoplasia within the delivery room. Of survivors, CPAM resection was performed within the first 2 years of life in 5 patients. One patient underwent resection at birth via an ex utero intrapartum treatment procedure for severe tracheal compression and mediastinal shift that was expected to cause difficulty with ventilation (case #5).

Median follow-up was 18 months (range, 4–36 months). Three children had respiratory symptoms: one with chronic lung disease and was below the 5th percentile for growth, the second had a tracheostomy in place and was tolerating both oral and tube feeds, and the third had intermittent asthmatic symptoms occasionally requiring a nebulizer. Two children were asymptomatic (Table 3).

3. Discussion

The current report summarizes the cumulative experience from two fetal treatment centers of patients presenting with high-risk

Table 2
Response to steroid administration.

Case	GA at 1st course of steroids	CVR response to 1st steroids course	Fluid response to 1st steroid course	GA at 2nd course of steroids	CVR response to 2nd steroid course	Fluid response to 2nd steroid course	Steroid courses (#)
1	19	"0"	"−"	21	"0"	"0"	4*
2	20	"−"	"0"	26	"+"	"+"	2
3	21	"−"	"−"	24	"0"	"0"	3*
4	19	"0"	"0"	21	"0"	"+"	2
5	30	"0"	"+"	35	"0"	"0"	2
6	22	"−"	"0"	23	"+"	"+"	2
7	19	"0"	"0"	22	"−"	"−"	2
8	26	"0"	"−"	28	"−"	"−"	2

GA, gestational age; CVR, congenital pulmonary airway malformation volume ratio. "+" indicates improvement, "0" stabilization, and "−" progression.
* Repeated courses of maternal betamethasone >2 given for lung maturation near time of delivery.