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Prenatal steroids for microcystic congenital cystic adenomatoid malformations

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Abstract

Objective: The purpose of this study is to evaluate the effect of prenatal steroid treatment in fetuses with sonographically diagnosed congenital cystic adenomatoid malformations (CCAMs).

Methods: This was an institutional review board–approved retrospective review of 372 patients referred to the University of California, San Francisco (UCSF), for fetal CCAM. Inclusion criteria were (1) a predominately microcystic CCAM lesion sonographically diagnosed at our institution, (2) maternal administration of a single course of prenatal corticosteroids (betamethasone), and (3) no fetal surgery. CCAM volume-to-head ratio (CVR), presence of hydrops, mediastinal shift, and diaphragm eversion were assessed before and after administration of betamethasone. The primary end points were survival to birth and neonatal discharge.

Results: Sixteen patients with predominantly microcystic CCAMs were treated with prenatal steroids. Three were excluded because of lack of follow-up information. All remaining fetuses (13/13) survived to delivery and 11/13 (84.6%) survived to neonatal discharge. At the time of steroid administration, all patients had CVR greater than 1.6, and 9 (69.2%) also had nonimmune hydrops fetalis. After a course of steroids, CVR decreased in 8 (61.5%) of the 13 patients, and hydrops resolved in 7 (77.8%) of the 9 patients with hydrops. The 2 patients whose hydrops did not resolve with steroid treatment did not survive to discharge.

Conclusion: In high-risk fetal patients with predominantly microcystic CCAM lesions, betamethasone is an effective treatment. This series is a pilot study for a prospective randomized trial comparing treatment of CCAM with betamethasone to placebo.

Congenital cystic adenomatoid malformations (CCAMs) are cystic lesions of the lung characterized by an excessive proliferation of terminal bronchioles and a lack of normal alveoli [1]. CCAMs are classified sonographically as either macrocystic, with one or more cysts greater than 5 mm in

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diameter, or microcystic lesions, which appear as solid, echogenic masses [2]. The study of CCAM, particularly the microcystic variant, is limited by a lack of appropriate animal models, but the pathogenesis of CCAM is believed to be related to dysregulation of cell proliferation and cell apoptosis in the terminal bronchioles [3].

The natural history of prenatally diagnosed CCAMs is variable, especially with respect to lesion growth between 18 and 28 weeks' gestation [4]. Routine sonographic evaluation during this period can be used to monitor growth of the CCAM. In most cases, lesion growth plateaus, or the lesion may even spontaneously regress [5-8]. However, a small number of lesions grow rapidly during this period, resulting in the development of fetal hydrops. Presence of hydrops with CCAM portends a poor outcome, with mortality up to 100% [2,9,10].

Because of the poor outcomes associated with fetal CCAM with hydrops, fetal intervention has been undertaken for fetuses with hydrops or on track to develop hydrops. Macrocystic CCAMs containing one or more large cysts are amenable to thoracoamniotic shunting or cyst aspiration [11]. Microcystic CCAMs typically require open fetal surgery with resection of the lesion to improve outcomes [12,13].

Previously, we reported our early experience with the administration of prenatal corticosteroids for treatment of severe microcystic CCAM with hydrops fetalis [14]. Other studies have further evaluated the decrease in relative CCAM size and resolution of hydrops after steroid administration in this patient population [15,16]. We now report the effects of prenatal corticosteroids on lesion growth, resolution of hydrops, and postnatal survival from our recent experience treating microcystic CCAMs. Although the mechanism of steroids' effect on CCAM is unknown, we hypothesize that the pulmonary cells in microcystic CCAMs are immature and that steroids stimulate their maturation.

1. Methods

1.1. Study design

This is an institutional review board–approved retrospective review of all consecutive cases of pregnancies complicated by CCAMs referred to the University of California, San Francisco (UCSF), from 1997 to 2008. After referral to our center, all patients underwent diagnostic high-resolution transabdominal ultrasound to confirm the diagnosis of a fetal CCAM. Patients were counseled on the prognosis of their pregnancy and offered intervention accordingly.

Inclusion criteria for this study were (1) a predominately microcystic CCAM lesion sonographically diagnosed at our institution, (2) maternal administration of a single course of prenatal steroids, and (3) no fetal surgical intervention for CCAM. Microcystic lesions were defined as predominantly (>50%) echogenic on sonographic evaluation. Patients without pregnancy follow-up data or with other sonographically diagnosed anomalies were excluded from this analysis. Position and volume of the mass, presence of nonimmune hydrops fetalis, degree of cardiac shift, and diaphragmatic eversion were determined from the pre- and posttherapy ultrasounds. Hydrops fetalis was defined as at least 2 of the following: ascites, integumentary edema, pericardial effusion, pleural effusion, or placentomegaly.

The CCAM volume-to-head circumference ratio (CVR) was calculated by dividing the volume of the mass (length × width × height × 0.52) by the head circumference [17] (Fig. 1). CVR measurements were calculated from all available ultrasounds conducted at our institution for patients who met inclusion criteria for this study. Patients with a microcystic CCAM in the presence of fetal hydrops and/or CVR greater than 1.6 were offered treatment with steroid therapy.

1.2. Description of technique

Patients who elected to undergo steroid treatment of CCAM after counseling at our center were administered a standard regimen of prenatal steroids (betamethasone, 12 mg intramuscularly, 2 doses with 24-hour separation). In 3 cases, betamethasone was administered prophylactically to stimulate lung maturation in preparation for fetal surgery, but ultimately, surgery was declined or not offered after further evaluation. Thirteen cases were administered betamethasone therapeutically for treatment of a predominantly microcystic CCAM with hydrops and/or CVR greater than 1.6. All patients received postadministration ultrasounds at our institution. After administration, patients returned to their primary care physician for routine ultrasound monitoring for the remainder of their pregnancy.

2. Results

A total of 372 fetuses with CCAM were referred to the UCSF Fetal Treatment Center for evaluation between 1997 and 2008. Sixteen pregnancies met the inclusion criteria of sonographically diagnosed predominately microcystic CCAM treated with a single course of prenatal steroids. Three pregnancies were excluded from this analysis because of lack of neonatal follow-up data. All pregnancies that received steroids in conjunction with fetal surgery were excluded from this analysis. The mean gestational age at steroids administration was 24.55 ± 1.53 weeks. These pregnancies were initially followed after steroid administration at our center, but then returned to their referring primary care obstetrician or maternal-fetal medicine specialist for continued evaluation.

Thirteen patients received a course of betamethasone for treatment of a predominantly microcystic CCAM with fetal hydrops and/or CVR greater than 1.6. Of the 13 fetuses, 9 (69.2%) were hydropic and 2 demonstrated ascites without

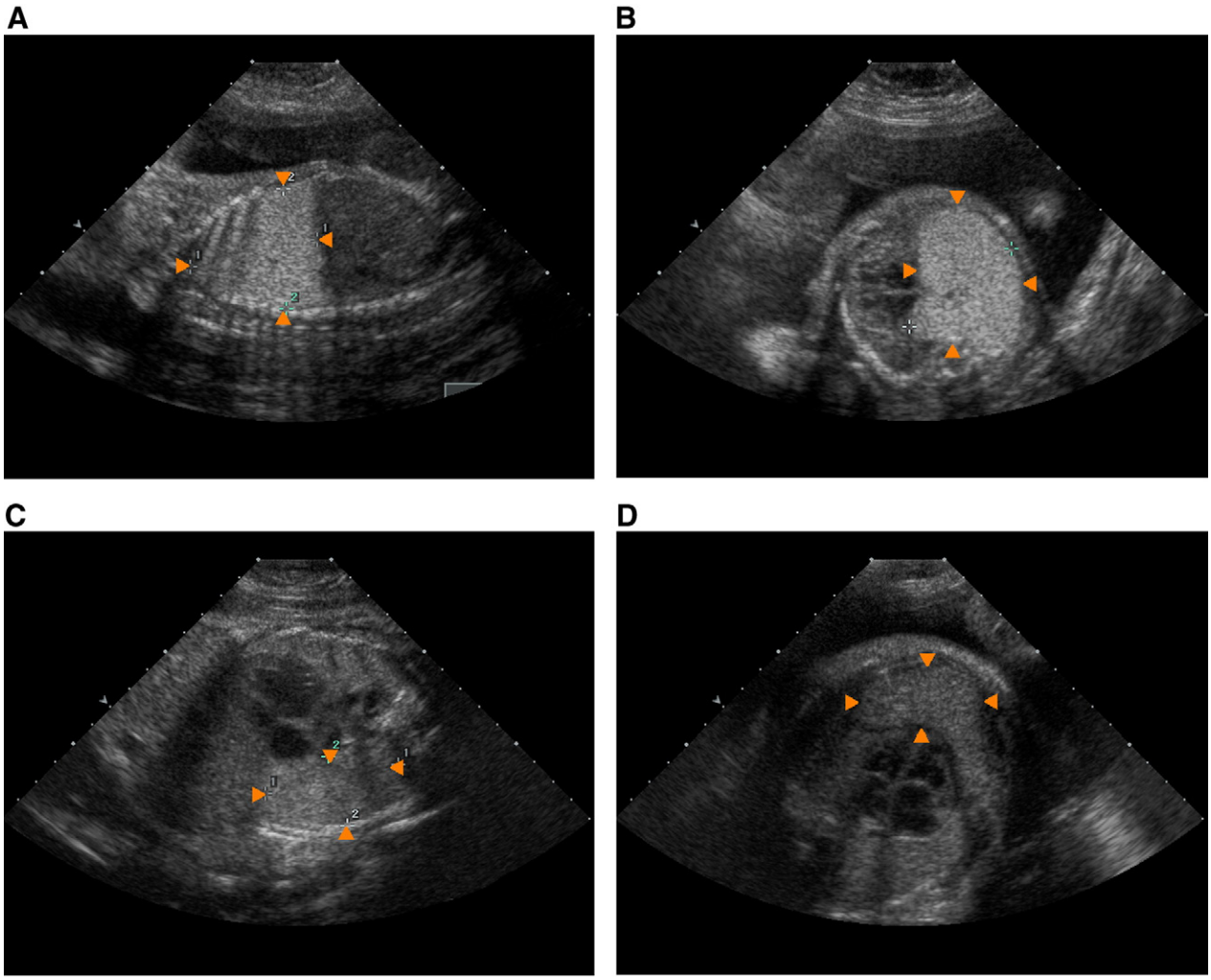

Fig. 1 Sagittal (A) and transverse (B) view of microcystic CCAM with CVR at 2.3 at 26 4/7 weeks' gestation with severe cardiac shift and diaphragm flattening. Sagittal (C) and transverse (D) view of the same fetus after steroid administration with CVR at 0.8 at 36 3/7 weeks' gestation demonstrating decreased size of mass, diaphragmatic eversion, and cardiac shift.

other evidence of hydrops at the time of treatment (Table 1). Hydrops completely resolved in 7 (77.8%) of the 9 hydropic fetuses, and ascites resolved in the 2 fetuses with ascites only. The mean interval between steroid treatment and resolution of hydrops was 29.9 days. The 2 fetuses whose hydrops did not resolve were delivered shortly after administration of betamethasone (mean, 11 days) because of spontaneous premature rupture of membranes (PROMs) and did not survive to discharge.

All patients had a CVR greater than 1.6 at the time of steroid administration (mean, 2.72 ± 0.92), and all demonstrated a degree of cardiac displacement and diaphragmatic eversion because of the presence of a large lesion in the thoracic cavity. After steroid treatment, lesion growth slowed in 8 (61.5%) of the 13 patients, as demonstrated by decreasing CVR measurements (mean CVR decrease, 1.6 ± 1.1). In 3 of the 8, lesions were determined to have regressed completely and were not identifiable on follow-up ultrasound. Over the course of follow-up, all patients with a decreasing CVR trend also demonstrated improved mediastinal shift, attributed to the decreasing size of the mass.

All 13 fetuses survived to delivery, and 11 (84.6%) survived to neonatal discharge. Eight patients delivered at term and mean gestational age at delivery of all fetuses was 35.6 weeks (range, 24 2/7 to 40 2/7 weeks). Three mothers (23.1%) experienced PROM at 9, 13, and 14 days after steroid administration. Two of these fetuses were delivered before 2/5 weeks' gestation and died within 1 hour of life; the third was delivered at 28 2/7 weeks and was discharged after 36 days.

3. Discussion

Prenatal management of CCAMs is determined by the size and classification of the lesion as well as the presence of fetal hydrops. Expectant management with frequent sonographic evaluation is appropriate for small, nonhydropic

Table 1 Summary of prenatal findings and outcomes of patients treated with steroids for high-risk CCAMs

Patient	Location	GA (at steroids) (wk)	Mediastinal shift (at steroids)	Hydrops (at steroids)	CVR (at steroids) (cm^2)	Hydrops resolved (GA) (wk)	GA (delivery) (wk)	Outcome
1	Right	26 4/7	Yes (cardiac shift, diaphragm eversion)	Yes (ascites, placentomegaly)	2.2	31 4/7	39	SVD at 39 wk, no resection, alive
2	Right	24	Yes (cardiac shift, diaphragm eversion)	Yes (ascites, pleural effusion)	3.4	24 5/7	40	SVD at 40 wk, RLL at 2.5 y, alive
3	Right	22 3/7	Yes	Yes (ascites, integumentary edema, placentomegaly)	5.0	No	24 2/7	Delivered at 24.2 wk for PROM, died on DOL1
4	Right	22 5/7	Yes	Yes (ascites, integumentary edema)	1.7	35 5/7	35 5/7	SVD at 34.9 wk, alive
5	Left	23 3/7	Yes (cardiac shift, diaphragm eversion)	Yes (ascites, pleural effusion, pericardial effusion)	2.0	28 1/7	39	SVD at 39.4 wk, alive
6	Left	24 1/7	Yes (cardiac shift, diaphragm eversion)	No (ascites)	3.5	26 6/7	38 2/7	SVD at 38.3 wk, alive
7	Right	26 2/7	Yes (cardiac shift, diaphragm eversion)	Yes (pericardial effusion, placentomegaly)	2.5	28 2/7	28 2/7	SVD at 28.3 wk for PROM, RLL at DOL5, alive
8	Left	25 3/7	Yes (cardiac shift, diaphragm flattened)	No (ascites)	3.3	29 1/7	40	Cesarean delivery at 40 wk, LLL at 6 mo, doing well
9	Right	27 1/7	Yes (cardiac shift)	No	2.3	–	40 2/7	SVD at 40.3 wk, alive
10	Right	23 6/7	Yes (cardiac shift, diaphragm eversion)	Yes (ascites, pleural effusion, pericardial effusion)	2.7	27	34 4/7	Cesarean delivery at 34 *, RLL at DOL14, alive
11	Right	24 4/7	Yes	No	1.8	–	39 4/7	SVD at 39.6 wk, alive
12	Left	25 4/7	Yes (cardiac shift)	Yes (ascites, pleural effusion, pericardial effusion)	1.9	26 6/7	40 2/7	SVD at 40.3 wk, alive
13	Left	23	Yes (cardiac shift, diaphragm eversion)	Yes (ascites, placentomegaly)	3.0	No	24 2/7	SVD at 24. 3 wk for PROM, died DOL1

GA indicates gestational age; SVD, spontaneous vaginal delivery; DOL, day of life; RLL, right lower lobectomy; LLL, left lower lobectomy.
*34 1/7 weeks.

CCAMs. However, in high-risk lesions (CVR >1.6 and/or hydrops), prenatal intervention may improve outcome. Macrocystic lesions are amenable to treatment via minimally invasive techniques, such as placement of thoracoamniotic shunts and cyst aspiration, with cumulative survival rates in hydropic fetuses of 50% and 69%, respectively [11]. Microcystic lesions require open fetal resection in the presence of fetal hydrops, with a survival rate of 52% and mean gestational age at delivery of 31.3 weeks [9,12,13,17]. Because morbidity and mortality remain high with intervention, there continues to be an impetus to develop better and less invasive techniques to treat high-risk lesions.

Table 2 Fetal microcystic CCAMs treated with steroids, data from 3 centers

Study	Patients	GA (at steroids) (wk)	CVR (at steroids)	Hydrops (at steroids)	Hydrops resolved	GA (delivery) (wk)	Survival
UCSF	13	24.6 ± 1.5	2.7 ± 0.9	9 (69.2%)	7 (77.8%)	35.6 ± 6.1	11
Peranteau et al [15]	10	23.0 ± 2.4	2.2 ± 0.9	5 (50.0%)	4 (80.0%)	38.4 ± 2.1	10
Morris et al [16]	8	23.6 ± 4.0	2.5 ± 1.5	6 (75.0%)	5 (83.3%)	36.2 ± 4.0	6
Total	31	23.8 ± 2.6	2.5 ± 1.0	20/31 (64.5%)	16/20 (80.0%)	36.7 ± 4.6	27/31 (87.1%)

GA indicates gestational age.

Table 3 Multicenter analysis of outcomes in fetuses with and without hydrops

	No hydrops	Hydrops	Hydrops, resolved	Hydrops, persistent
Survival	11 (100.0%)	16 (80.0%)	15 * (93.8%)	1 * (25.0%)
GA (delivery) (wk)	39.0	36.0	37.0 *	28.9 *

	Survival	GA (delivery) (wk)
No hydrops	11 (100.0%)	39.0
Hydrops	16 (80.0%)	36.0
Resolved	15 * (93.8%)	37.0 *
Persistent	1 * (25.0%)	28.9 *

GA indicates gestational age.
* $P < .05$ by χ^2 analysis.

Recently, several institutions reported their experience with the use of prenatal steroids for fetal lung masses. We first reported our initial experience of prenatal steroid administration for CCAM in 2003 [14]. In a cohort of 3 hydropic patients with large microcystic CCAMs, we observed resolution of hydrops and survival through the neonatal period after maternal steroid administration. Subsequently, Peranteau et al [15] reported 100% survival in a cohort of 11 fetuses with high-risk CCAM lesions (10/11 microcystic). They observed decreased lesion growth rates in 8 of 11 fetuses and resolution of hydrops in 4 of 5 fetuses. Most recently, Morris et al [16] reported the application of this therapy for both macrocystic and microcystic lesions. For patients with microcystic lesions, they reported 75% survival (6/8) and resolution of hydrops in 66% (4/6). Their experience with steroids for macrocystic CCAMs was less favorable. Of the 6 patients with macrocystic lesions and hydrops treated with steroids, only one patient survived through the neonatal period, with resolution of hydrops at 63 days after administration.

In the present study, we report our recent institutional experience with the administration of prenatal steroids to treat high-risk (CVR >1.6 and/or hydrops) fetal CCAMs. We observed an overall survival to discharge of 84.6% with resolution of hydrops in 77.8% in fetuses with predominantly microcystic lesions after administration of a single course of prenatal steroids. Of note, 3 patients delivered shortly after steroid administration because of PROMs. Two of these fetuses delivered before viability and died because of respiratory failure. Our data, as with all currently available data on the prenatal management of CCAM, are limited by the retrospective nature of the study. Similarly, although all patients were followed sonographically at our institution immediately after steroid administration, many returned to their primary care obstetrician for prenatal management and delivery, limiting analysis of these data.

Incorporating our data with previous reports, there are 31 cases of microcystic CCAM lesions treated with steroids in the literature. Overall survival to discharge is 87.1%, and resolution of fetal hydrops is observed in 80% of these fetuses (Table 2). Hydrops at the time of steroid administration did not have a significant relationship with survival or gestational age at delivery (Table 3). There was, however, a significant difference ($P < .05$) in outcomes between those fetuses whose hydrops resolved and those whose hydrops was persistent after steroid therapy. These data are promising, especially compared with historic controls in which up to 100% mortality with hydrops and 56% mortality with a CVR greater than 1.6 have been reported [10,11,17]. Although the mechanism of this therapy remains unknown, these cumulative data suggest that steroid therapy is superior to fetal surgery for hydropic microcystic CCAMs. Survival with steroid therapy is substantially higher (87.1% vs approximately 50%), and steroid therapy incurs very little maternal risk.

Our findings support the routine use of prenatal steroids for hydropic microcystic CCAMs. The question remains, however, whether large microcystic CCAMs, in the absence of hydrops, should be treated with steroids. The natural history of these lesions has been reported previously with variable outcomes. Several studies have reported spontaneous decrease in CCAM growth or resolution in nonhydropic lesions [4,6,8]. In other cases, mass effect because of the large CCAM results in the development of fetal hydrops. Therefore, it is unknown if steroid administration is helpful in nonhydropic large microcystic lesions. A multicenter randomized clinical trial comparing maternal steroid administration to placebo for large microcystic CCAMs has been proposed for investigation of this therapy.

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