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Perinatal outcomes of prenatal diagnosis of congenital pulmonary airway malformation: an experience

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SUMMARY

OBJECTIVE: This study aimed to assess the perinatal outcomes of pregnancies with a prenatal diagnosis of congenital cystic adenomatoid malformation.

METHODS: We conducted a retrospective cohort study based on information contained in the medical records of pregnant women whose fetuses had been prenatally diagnosed with congenital cystic adenomatoid malformation by ultrasonography.

RESULTS: Sample analysis was based on 21 singleton pregnancies with confirmed isolated fetal congenital cystic adenomatoid malformations. The mean maternal±standard deviation age was 28±7.7 years. Types I, II, and III congenital cystic adenomatoid malformation were detected in 19% (4/21), 52.4% (11/21), and 28.6% (6/21), respectively. All fetuses presented with unilateral congenital cystic adenomatoid malformation (21/21) without associated anomalies, and 52.3% (11/21) were in the right lung. In total, 33.3% (7/21) of fetuses presented a "congenital cystic adenomatoid malformation volume ratio" >1.6 and were managed with maternal betamethasone administration. The mean gestational age at the time of steroid administration was 28.5±0.9 weeks, with a reduction in the lesion dimensions of 9.5% (2/21) (Types I and III of congenital cystic adenomatoid malformation). The mean gestational age at delivery was 38.7±2.4 weeks, and a cesarean section was performed in 76.2% (16/21) cases. Postsurgical resection was necessary for 23.8% (5/21) of the patients, and 4.7% (1/21) of them died because of respiratory complications after surgery. Pulmonary hypoplasia occurred in 9.5% (2/21) of the patients, and 4.7% (1/21) of them died because of respiratory insufficiency. The survival rate was 90.5% (19/21), and 57.2% (12/21) remained asymptomatic.

CONCLUSION: Despite the isolated prenatal diagnosis of congenital cystic adenomatoid malformation, which showed good survival, congenital cystic adenomatoid malformation is associated with significant perinatal morbidity. Maternal betamethasone administration did not significantly reduce fetal lung lesion dimensions.

KEYWORDS: Prenatal diagnosis. Cystic adenomatoid malformation of lung, congenital. Ultrasonography. Perinatal mortality.

INTRODUCTION

Congenital cystic adenomatoid malformation (CCAM) is a multicystic mass of pulmonary tissue, with an incidence of approximately 1:25,000 to 1:35,000[1]. This may represent a failure in the developmental phase of terminal bronchiolar structures, which occurs between the fifth and sixth weeks of gestation during the pseudo-glandular phase of the lung[2,3]. CCAM is somewhat more common in male fetuses and can even occur in any lung lobe, being unilobar in 80–95% of cases and bilateral in less than 2%[4]. The CCAM communicates with the tracheobronchial tree, although this route can be irregular and tortuous. In general, CCAM shows normal pulmonary vascularization, although anomalous vascularization has been reported[5].

Due to routine fetal anomaly scanning and advances in antenatal ultrasonography, CCAM has been increasingly diagnosed[6]. Thus, it is possible to evaluate the lesion type and size, as well as the presence of mediastinal shift, fetal hydrops, or massive fluid retention. Three main types can be identified by ultrasonography: Types I and II as cystic, fluid-filled masses and Type III as a solid mass[5]. The natural history of CCAMs involves intrauterine growth until 28 weeks of gestation, at which growth plateaus or even regresses[7]. Ultrasound findings are important to predict the prognosis and management of CCAM since the presence of larger cysts and/or fetal hydrops are considered high risk and are frequently associated with a poorer prognosis[8,9]. In this situation, antenatal betamethasone is the first-line therapy, while open fetal surgical resection and/or an additional course of steroids are used as alternative treatment options[8-10].

In this report, we evaluated the perinatal outcomes of pregnancies with prenatal diagnoses of CCAM.

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METHODS

We conducted a retrospective cohort study based on information from medical records of pregnant women whose fetuses had been prenatally diagnosed by ultrasonography with CCAM at the Department of Obstetrics, Paulista School of Medicine, Federal University of São Paulo (EPM-UNIFESP), between November 2013 and July 2017. This study was approved by the Research Ethics Committee of UNIFESP (file: CAE 29171319.4.0000.5505).

Inclusion criteria were (1) singleton pregnancy with a live fetus and (2) CCAM lesion diagnosed by ultrasound at our institution (with or without maternal administration of prenatal corticosteroids). Exclusion criteria were (1) the presence of other congenital malformations, (2) intrauterine fetal death, and (3) unavailable data from the postnatal evaluation.

To perform this study, the following variables were evaluated: maternal age, number of pregnancies and deliveries, gestational age at birth, number of ultrasound examinations during the prenatal period, classification of CCAM according to Stocker et al.[4], the use of antenatal betamethasone, birth weight, type of delivery, gender of the neonates, Apgar scores at the first and fifth minutes in the neonatal intensive care unit, type and localization of the CCAMs, postnatal complications, and hospitalization in childhood.

The data were collected using an Excel 2007 spreadsheet (Microsoft Corp., Redmond, WA, USA). For statistical analysis, continuous variables were presented as mean and standard deviation (SD), and data were compared using the unpaired Student's t-test. Categorical variables were expressed as numbers and percentages and analyzed for comparisons using the Pearson's chi-square test.

RESULTS

During the study period, 27 pregnancies with fetal CCAM were examined. Six cases were excluded: one twin pregnancy, two presenting with other malformations, and three lost to follow-up. Therefore, our statistical analysis was based on 21 singleton pregnancies with confirmed isolated fetal CCAM diagnosed between 22 and 32 weeks of gestation (Table 1). The mean maternal±SD age was 28±7.8 years, with a range of 18–44 years. The mean of previous deliveries±SD was 1±1.3, with a range of 0–4. According to the classification by Stocker et al.[4], 19.0% (4/21) were Type I, 52.4% (11/21) were Type II, and 28.6% (6/21) were Type III. The mean of ultrasound examinations±SD was 4.1±1.4, with a range of 2.0–6.0. The mean gestational age at the last ultrasound examination±SD was 36.2±1.8 weeks, with a range of 32.1–39.4 weeks, and the mean CCAM volume±SD was 10.7±15.1 cm^3, with a range of 0–57.3 cm^3. The last ultrasound examination did not identify lesions in 5 (23.8%) cases (Table 1).

All CCAMs were unilateral (21/21) without associated anomalies, and 52.3% (11/21) were in the right lung. Of the fetuses, 33.3% (7/21) presented signs of increased risk for fetal hydrops or lesions with "CCAM volume ratio" (CVR) [length (cm)×height (cm)×width (cm)×0.52/head circumference (cm)] >1.6 after lesion growth plateau (28 weeks of gestation). For this reason, these fetuses were managed with prenatal steroids (a single course of betamethasone, 12 mg intramuscularly, two doses, and 24 h apart), but the prenatal intervention was not needed. The mean gestational age at the time of steroid administration±SD was 28.5±0.9 weeks, with a range of 28.0–30.1 weeks. Subsequently, the fetal lung lesions exhibited a 9.5% (2/21) reduction in dimensions (Types I and III CCAM). The fetal lung lesion increased in 14.3% (3/21) of the cases (all were Type III CCAM) and 9.5% (2/21) remained the same size (Figure 1).

Table 1. Clinical data of congenital cystic adenomatoid malformation.

Characteristics	Mean (standard deviation)
Maternal age (years)	28 (7.8)
Number of pregnancies	2 (1.5)
Parity	1 (1.3)
Body mass index (kg/m^2)	29.1 (3.9)
Ultrasound examinations	4.1 (1.4)
Gestational age at last scan (weeks)	36.2 (1.8)
CCAM volume (cm^3)	10.7 (15.1)
Gestational age at delivery (weeks)	38.7 (2.4)
Birth weight (g)	3158.1 (658.0)
Apgar scores at the first minute	7.8 (1.8)
Apgar scores at the fifth minute	8.7 (1.1)
Total (n)	21
Percentage (%)	
Delivery	
Cesarean section	76.2
Vaginal	23.8
Gender	
Male	52.4
Female	47.6
Side affected	
Right lung	52.3
Left lung	47.7
Total (%)	100

Cesarean section was performed in 76.2% (16/21) of the cases, and 23.8% (5/21) were vaginal deliveries. The mean gestational age at delivery±SD was 38.7±2.4 weeks, with a range of 31–41 weeks. In 90.5% (19/21) of the cases, delivery occurred at >37 weeks and 57.1% (12/21) at >39 weeks. The mean birth weight±SD was 3158.1±658.0 g, with a range of 1705.0–4795.0 g (Table 1). The mean Apgar scores±SD at the first and fifth minutes were 7.8±1.8 and 8.7±1.1, respectively, with 81.0% of them being >9. In terms of gender, 52.4% (11/21) were male and 47.6% (10/21) were female (Table 1).

Postsurgical resection was necessary for 23.8% (5/21) of the patients, and 4.7% (1/21) died because of respiratory complications after surgical resection. Recurrent pneumonia occurred in 9.5% (2/21) of the patients. Pulmonary hypoplasia occurred in 9.5% (2/21) of the patients, and 4.7% (1/21) of the patients died because of respiratory insufficiency. The survival rate was 90.5% (19/21), and 57.2% (12/21) of the patients remained asymptomatic. A total of 33.4% (7/21) received betamethasone as a maternal therapeutic option during the prenatal period, and 24.6% (6/21) survived (Table 2).

DISCUSSION

CCAM is a malformation originating from abnormal airway development, wherein the terminal bronchioles proliferate abnormally at the beginning of embryonic development, generating intraparenchymal cysts of varying sizes[11,12]. Many congenital abnormalities can be identified and managed owing to advances in prenatal diagnostics and sonographic improvements. According to the literature, the antenatal diagnosis rate can reach 85%[11], and the majority of lung cysts can be detected with routine ultrasounds during the 18–20 weeks of gestation[8]. However, in our study, all cases of CCAM were diagnosed after 20 weeks of gestation. Fetal magnetic resonance imaging is not demonstrably better than ultrasound for the evaluation of this pathology[13].

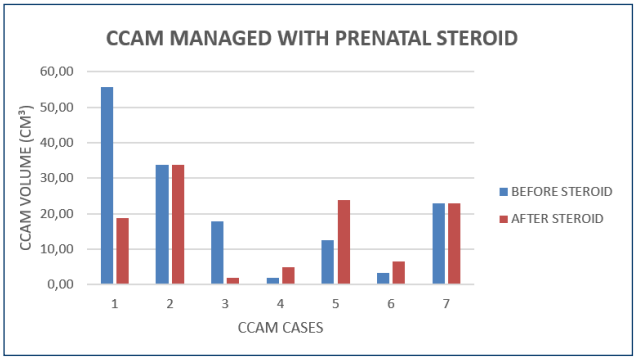

Figure 1. Congenital cystic adenomatoid malformation volume before (blue bar) after (red bar) steroid administration. Cases according to Stocker et al.'s[4] classification: Type I: 4, 5, and 6; Type II: 1 and 2; Type III: 3 and 7.

According to the Stocker et al.'s[4] classification, CCAM can be subdivided into three types. Type I has a good prognosis, is present in about 50% of cases, and consists of single or multiple cysts of larger dimensions (usually >2.0 cm), filled with air or fluid. They appear to communicate with the normal lung parenchyma and may be surrounded by smaller cysts. Type II lesions occur in approximately 40% of cases and consist of numerous small cysts (<2.0 cm) mixed with areas of increased echogenicity on ultrasound. The prognosis depends on the severity of the lesion and its association with other fetal malformations. There is a strong association between congenital anomalies and Type II CCAM, the main ones being genitourinary, such as renal dysgenesis or agenesis, and cardiac, such as tetralogy of Fallot and truncus arteriosus; others include diaphragmatic hernia and musculoskeletal anomalies. Type III is a solid mass that contains very small cysts (<5.0 mm)[4].

We observed that in ultrasound examinations, Type II was the main type of CCAM, corresponding to 52.4% of the cases, which disagrees with the findings of Mehta et al.[2], wherein Type I was more common. All cases were unilateral, localized, and not accompanied by other malformations. CCAMs usually grow until 28 weeks of gestation when it reaches a plateau and may regress in size. However, in some cases, the lesion can grow rapidly, causing the mediastinal shift, polyhydramnios, nonimmune fetal hydrops, and even fetal death[7].

Ultrasound evaluation should be performed weekly to assess the CCAM volume, and CVR may identify early signs

Table 2. Perinatal outcomes following prenatal diagnosis of congenital cystic adenomatoid malformation using or not maternal steroid administration.

Maternal therapeutic	Asymptomatic	Perinatal outcomes of CCAM			Total
		Neonatal resection	Pulmonary hypoplasia	Recurrent pneumonia	
With betamethasone	3 (14.3%)	3 (14.3%)	1* (4.7%)	0 (0%)	7 (33.4%)
Without betamethasone	9 (42.9%)	2 (9.5%)	1 (4.7%)	2 (9.5%)	14 (66.6%)
Total	12 (57.2%)	5** (23.8%)	2 (9.5%)	2 (9.5%)	21 (100.0%)

*One death after surgery by respiratory complications. **One death by respiratory insufficiency.

of fetal hydrops. Crombleholme et al.[14] showed that CVR >1.6 proved to be a good predictor of fetal hydrops and perinatal mortality. If there are any dominant cysts, even with a CVR <1.6, there is a risk of acute cyst growth and development of fetal hydrops. A thoracoamniotic shunt may be considered if signs of fetal decompensation at <32 weeks' gestation are identified[15]. Microcystic lesions increase the risk of fetal hydrops, pulmonary hypoplasia, and polyhydramnios[16].

Although the mechanism is unknown, the maternal use of corticosteroids has been performed in pregnancies with CCAM in an attempt to reduce the size of the lesion and reverse fetal hydrops. Curran et al.[17] evaluated the effect of prenatal use of a single cycle of steroids in patients with predominantly microcystic lesions and/or a CVR >1.6. Lesion reduction was observed in 61% of the cases, and fetal hydrops was resolved in 78%. The neonatal survival rate is approximately 85%. In this study, 33.3% of the fetuses showed signs of increased risk of fetal hydrops/lesions, had a CVR >1.6, and their mothers received corticosteroid therapy with betamethasone while pregnant. Post-therapy, almost 50% of the fetuses had no progression/increase of CCAM, although most cases were Type II, and none required prenatal intervention.

It is important to emphasize the limitation of this study in defending the use of corticosteroids as therapy, which was not proven, because of the small sample size. However, as it is a rare disease, it may encourage the development of more representative multicenter studies.

CONCLUSION

Despite the isolated prenatal diagnosis of CCAM that showed good survival, CCAM is associated with significant perinatal morbidity. Maternal betamethasone administration did not significantly reduce fetal lung lesion dimensions. More studies are needed to determine whether or not to encourage steroid therapy in an attempt to reduce the size of the lesion and reverse fetal hydrops.

AUTHORS' CONTRIBUTIONS

LCR: Conceptualization, Formal Analysis, Project administration, Visualization. **GDR:** Data curation, Visualization. **TDM:** Investigation, Validation, Visualization. **LGC:** Data curation, Investigation, Methodology. **EAJ:** Supervision, Visualization, Writing – review & editing. **JVJC:** Visualization, Writing – original draft.

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