

## Intrauterine Treatment of a Fetal Lymphangioma With OK-432 May be not Effective

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### Abstract

We report the case of a fetal neck lymphangioma which was treated antenatally due to an increase in the growth of the lesion. A single intracystic injection of OK-432 was performed at 31 weeks of gestation. The effects of therapy in infant were an increased echogenicity and a slight decrease in the tumor size. The same treatment was continued after the birth, but with a poor response. No complications from antenatal treatment were observed.

**Keywords:** Fetal therapy – Medical; Fetal therapy – Surgical; Cordocentesis; 2nd Trimester Ultrasound Screening for Aneuploidy and Anomalies

### Case Report

A 28-year old woman was referred to our unit at 27 weeks of gestation because of an ultrasound finding of a fetal neck mass. Ultrasound examination performed in our department confirmed the presence of a poorly vascularized multicystic mass of 4 cm on the anterior of the fetal neck. Based on ultrasound appearance, a lymphangioma was considered. Other fetal anatomical structures and the amniotic fluid volume were normal. Amniocentesis performed during the hospitalization revealed a normal fetal karyotype (46 XY).

Three weeks later, at 30 weeks of gestation, the neck mass size had increased to 7,8 x 6 cm (figure 1). The amount of amniotic fluid remained normal. Because of the significant growth of the mass, intrauterine treatment was undertaken.

At 31 weeks of gestation around 35 ml of fluid was aspirated from the largest fetal neck cyst which was followed by injection of 10 ml of OK-432 (Picibanil) at a concentration of 0,01 mg/ml. To avoid fetal movement during the aspiration and injection the whole procedure was preceded by the direct administration of a muscle relaxation agent into umbilical vein. The intervention was uneventful. One day after the procedure an increased echogenicity of the cyst was noticed. Three weeks later, at 34 weeks, this increased echogenicity of the cystic mass was even more evident (figure 2). At that time, the mass size was 7,3 x 5,7 cm. At 37 weeks of gestation the mass size had decreased to 6,6 x 5,0 cm. Both in ultrasound and in MRI performed at that time there were no signs of fetal airways constriction.



**Figure 1:** The longitudinal view of the mass at 30 weeks gestation.

**Received date:** March 18, 2018

**Accepted date:** September 20, 2018

**Published date:** September 26, 2018

**Citation:** Kornacki, J., et al. Intrauterine Treatment of a Fetal Lymphangioma With OK-432 May be not Effective. (2018) J Environ Health Sci 4(2): 52- 54.

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**Figure 2:** The increased echogenicity of the mass at 34 weeks (3 weeks after injection of OK-432).

At 38 weeks of gestation, a live 3,310 – gram male infant with Apgar score of 7 and 9 at 1 and 5 min, respectively, was delivered by elective caesarean section. A left-sided neck lymphangioma was clinically evident at birth without any airway obstruction (figure 3).



**Figure 3:** The neck lymphangioma (an image taken on the day a baby was born).

After delivery, constant growth of the mass was observed. The patient was discharged home and scheduled for the sclerotherapy at the 30<sup>th</sup> day of life. At this time, ultrasound scans revealed a mixed, macro- and microcystic, structure of the lesion with the largest cyst measuring 4,5 x 1,8 cm. Three procedures of aspiration of the lymph and intracystic injections of OK 432 were performed at the 30<sup>th</sup> day of life, 3 months and 4,5 months. The volumes of the lymph obtained were 10 cc, 55 cc and 2 cc, the amounts of OK 432 administered were 2 KE, 3 KE and 1 KE, respectively (KE = Klinische Einheit). After sclerotherapies, the signs of inflammatory reactions such as mild fever and flushing were noted with no other local or general symptoms. At a 10 - month follow-up no shrinkage of the lymphangioma was observed. Otherwise, the patient had developed normally. Because of persisting significant deformation of the face patient was subjected to surgical treatment.

## Discussion

A differential diagnosis of a fetal neck tumor or cystic lesions include lymphangioma, haemangioma, goiter, neuroblastoma and teratoma (Kornacki, J., et al. 2011). Both ultrasound and magnetic resonance imaging (MRI) enable the differentiation between at least solid or partly solid tumors such as fetal goiter, teratoma or neuroblastoma and cystic or multicystic lesions (lymphangioma, hemangioma).

A diagnosis of a fetal neck lesion is always a serious clinical situation, that may be associated not only with cosmetic consequences for a child but also with life-threatening complications (Kornacki, J., et al. 2011). The most dangerous conditions associated with fetal neck tumors are secondary cardiac failure, typical for large, highly vascularized tumors such as goiter and acute postnatal respiratory distress due to airway compression (Kornacki, J., et al, 2011).

So far, there are no well established methods for the intrauterine treatment of most fetal neck tumors. The most effective one is probably the intra-amniotic therapy of fetal goitrous hypothyroidism with repeated intrauterine injections of L-thyroxine (Ribault, V., et al, 2009; Kornacki, J., et al. 2011). Another, more controversial method for the intrauterine treatment of fetal neck lesions, which is restricted to lymphangioma, is the intracystic injection of OK-432.

OK-432 is a sclerotherapy agent that was used for the first time in the postnatal treatment of a neck lymphangioma in 1987 (Ogita, S., et al. 1994). It is a lyophilized mixture of low-virulence group A *Streptococcus pyogenes* Su strain bacteria incubated with a low concentration of benzyl penicillin (Ogita, S, et al, 1996). The exact mechanism of its action is unknown, but the effectiveness of the drug is probably the consequence of its proinflammatory activity, including increased productions of various cytokines (Yang, K.D., et al. 1992; Narkio-Makela, M., et al. 2011).

So far, there is only one case report on the successful intrauterine therapy of a fetal neck lymphangioma by intracystic injection of OK-432 (Mikovic, Z., et al. 2009). The authors of this study described an almost complete disappearance of the lesions after single injections of OK-432 in two fetuses.

In comparison to the single study of the antenatal therapy of a neck lymphangioma with OK-432, postnatal treatment is widely used and accepted (Yoo, J.C., et al., 2009; Narkio-Makela, M., et al. 2011; Kim, D.W., 2014;). It became an effective and popular alternative to surgical treatment, and often more preferable to surgery because of its safety (Narkio-Makela, M., et al. 2011). The effectiveness of postnatal therapy after a single or repeated injection of OK-432, as reported by different authors, is around 70 - 80% (Yoo, J.C., et al., 2009; Kim, D.W., 2014) .

The two remaining reports on the antenatal use of OK-432 concern the rescue treatment of fetal chylothorax (Tanemura, M., et al. 2001; Lo, T.K., et al. 2012). In both studies, the authors observed a resolution of the fetal chylothorax after a single or repeated intra thoracic injections of OK-432.

In the clinical case presented by us, in comparison to the two cases described by Mikovic et al. (2009), we did not observe a resolution of the lesion after a single injection of OK-432. The only positive effect we observed was a slight and transient decrease in tumor size. We do not know if this had any

clinical significance, including the decreased risk of fetal airway obstruction.

More interestingly, no sufficient therapeutic effect was observed after the postnatal therapy. The reason for this may be the mixed, mostly microcystic character of the mass. In several studies the microcystic lesions were significantly more resistant to sclerotherapy with OK-432 than macrocystic one (Banieghbal, B., et al. 2003; Luzzatto, C., et al. 2005; Narkio-Makela, M., et al. 2011).

In microcystic lymphangioma, the access of drugs to cysts may be difficult and the connective tissue surrounding cysts makes the shrinkage of mass less effective (Banieghbal, B., et al. 2003; Luzzatto, C., et al. 2005).

## Conclusion

Despite the fact that lymphangioma may often not compress the fetal airways and this is why the anetnatal treatment is controversial, the very big, rapidly growing masses may theoretically cause postnatal acute respiratory failure of the fetus which life threatening condition. In the experienced hands, the intruterine therapy, if undertaken, is rather not associated with high complications rate and this is why may be eventually considered.

**Conflicts of Interest:** None.

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