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Letter

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A case report of sirolimus use in early fetal management of lymphatic malformation

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Sirolimus, by targeting the mammalian target of rapamycin (mTOR) pathway, has demonstrated efficacy on lymphatic malformations (LMs) in adults and neonates. The current hypothesis is that the earlier the lesion is treated, the better it responds. This has prompted the idea that sirolimus administration might be efficacious to treat fetal LMs as well. Here we report a successful management of a cervicofacial fetal LM with sirolimus taken orally by the mother from the 22nd week of pregnancy until 2 weeks before planned delivery. Repeated cordocentesis recorded a 30% transplacental crossing of sirolimus. Continuation of sirolimus after birth allowed resection of the residual mass. We have followed the physical and neurological evolution of the child for 6 years since the fetal administration of sirolimus. We conclude that early administration of sirolimus during pregnancy with maternal serum monitoring may be proposed to high-risk fetal LMs in selected cases.

Lymphatic malformations (LMs) result from locally abnormal lymphatic development. They occur as solitary lesions, commonly infiltrating soft tissues. They can be found anywhere in the body, from extremities to the abdominal and thoracic cavities.

LMs are non-cancerous lesions and expand with the growth of the child. Even if spontaneous regressions have been observed[1], LMs often result in severe complications, including organ dysfunction, pain and difficulties in breathing or swallowing[2,3]. Surgery and sclerotherapy are often challenging or unfeasible due to the extension of the lesion and involvement of surrounding structures[4].

Most LMs result from a somatic PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) activating mutation. The *PIK3CA* gene encodes the p110*α* catalytic subunit of PI3K, which leads to activation of AKT (protein kinase B) and locally induces excessive and anarchic lymphangiogenesis[5]. By targeting the mammalian target of rapamycin (mTOR) pathway, required for AKT activation,

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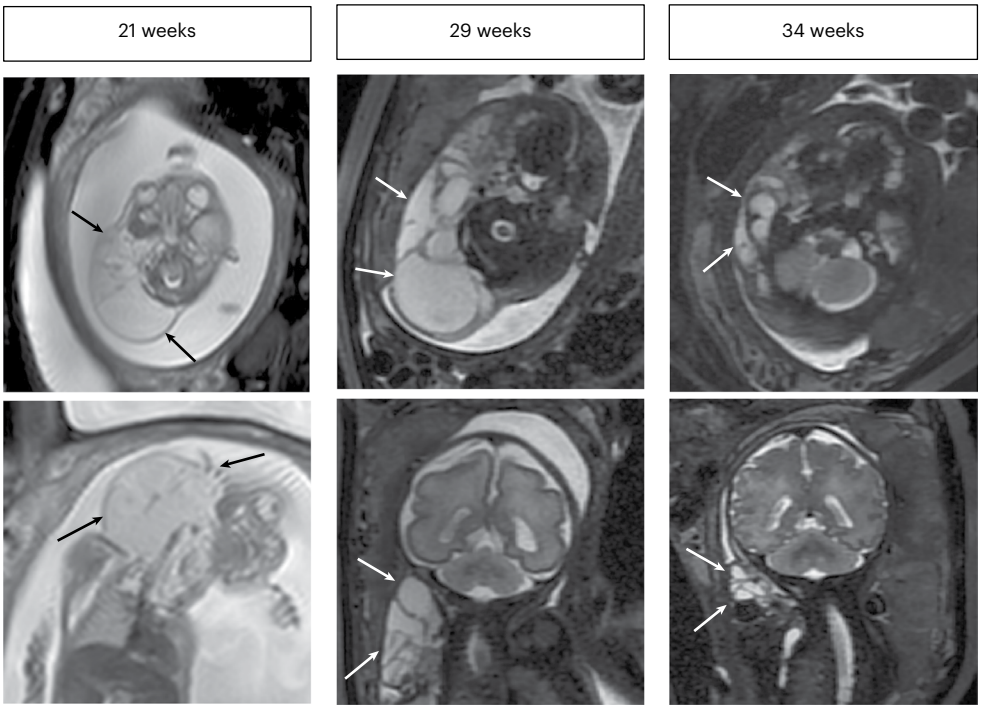

Fig. 1 | Intrauterine evolution. Fetal MRI of cervical LM (arrows) before sirolimus initiation (21 weeks of pregnancy) and on sirolimus (29 weeks and 34 weeks of pregnancy) in T2-weighted axial (upper) and coronal view (lower).

sirolimus has been shown to efficiently improve quality of life in children and adults with LM, reducing pain, improving functional limitation and decreasing the volume[6–8].

Half of LMs are diagnosed at birth, and 90% are diagnosed during the first 2 years of life. Prenatal ultrasonography (US) allows diagnosis of LM during fetal development[9]. A small and slowly progressing LM can be closely followed by US and magnetic resonance imaging (MRI) during pregnancy. However, the management of extensive and rapidly growing fetal LM is challenging due to the potential life-threatening complications, including polyhydramnios, preterm labor and delivery, pulmonary hypoplasia, fetal growth restriction and airway compromise. In addition, delivery can be complicated for the mother (dystocic vaginal delivery and abnormal position of the fetal head) and for the fetus (lesion-related bleeding), often requiring elective cesarean section.

Sirolimus has been used to manage fetal intra-cardiac rhabdomyoma related to tuberous sclerosis (TSC) via placental diffusion during five pregnancies[10,11]. Here we describe the in utero management of a fetus with a high-risk extensive cervicofacial LM diagnosed at 16 weeks of gestation, with sirolimus treatment started as early as 22 weeks of gestation. We report on the correlation between maternal and fetal sirolimus serum levels and the general development of the child during an over 6-year follow-up (Figs. 2 and 3).

Results

After informed consent approval, the mother started oral sirolimus with a loading dose of 6 mg d^{-1} for 3 d, followed by standard adult dosing of 2 mg daily. Five days after sirolimus initiation (week 23, day 1), the maternal serum level of sirolimus was 3 ng ml^{-1}, which led us to increase the dose of sirolimus to 3 mg d^{-1}, to reach the target serum level ranging between 10 ng ml^{-1} and 15 ng ml^{-1}. Two days later (week 23, day 2), the maternal serum sirolimus level increased to 5.8 ng ml^{-1}, and the fetal serum sirolimus level, obtained by cordocentesis, was 1.2 ng ml^{-1} (20% of maternal level). We, thus, increased the daily dose to 4 mg d^{-1}, which was effective in reaching the maternal target level of 15.6 ng ml^{-1} (attainable at week 24, day 5). At this level, a rapid decrease in the volume of the LM was noted from 357 cm^3 at week 24, day 2 (US) to 272 cm^3 at week 25, day 4 (US), 250 cm^3 at week 28, day 2 (US), 150 cm^3 at week 29, day 1 (MRI) and 50 cm^3 at week 34, day 1 (MRI) (Fig. 2).

The increase in maternal serum level was associated with an increase in fetal serum level that reached 4.7 ng ml^{-1} at week 25, day 2 (28% of maternal level). Sirolimus was well tolerated by the mother with grade 2 (Common Terminology Criteria for Adverse Events version 5) mucositis lasting 5 d and responsive to supportive care. No identified side effects were noted in the fetus, such as growth restriction or other developmental anomalies. As the LM volume decreased substantially with no further threat to the fetus, sirolimus was discontinued 2 weeks before the planned cesarean delivery (week 39) to prevent potential maternal wound healing issues. The delivery was uncomplicated. Birth weight of the baby girl was 2,900 g, and Apgar scores were 9/8/10.

At birth, clinical examination revealed the remains of an LM extending from the right postero-lateral cervical region to the homolateral axilla and chest wall; a partial facial paresis was also observed and explained by intrauterine neurological compression by the LM (Fig. 3). Intubation was not needed. At 3 d of age, the LM started to increase in size progressively, resulting in breathing difficulties (stridor, SO_2: 90–94%, obstructive apnea), bradycardia and feeding difficulties. An MRI, at day 4, confirmed LM progression with left tracheal shift, extension to the pterygo-maxillary fossa and posterior side of the pharynx and involvement of the superior mediastinal vessels, such as brachio-cephalic trunk, superior vena cava, azygos vein and the aortic arch (Fig. 3).

Sirolimus was started at a dose of 0.1 mg twice a day (0.5 mg m^{-2} twice a day) with co-trimoxazole prophylaxis. The LM volume and feeding and breathing difficulties decreased rapidly. Weight and height increased progressively following the P25 curve. Residual cervical mass caused progressive head tilt and difficulties in the sitting position, requiring physiotherapy sessions that started at 4 weeks of life. At 11 months, while on sirolimus, bleomycin-based sclerotherapy was

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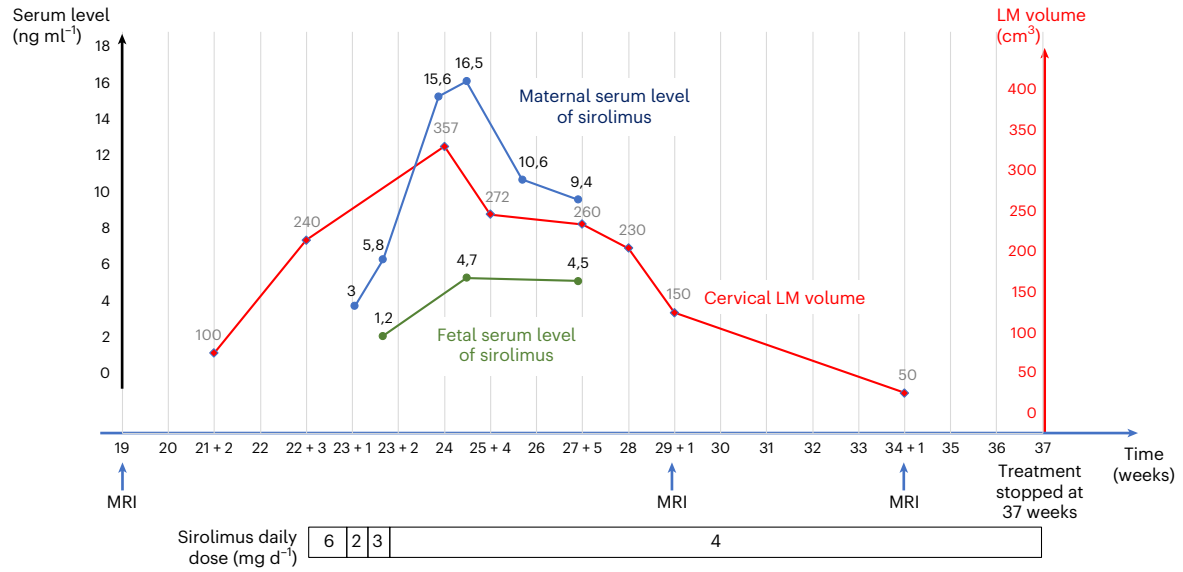

Fig. 2 | LM evolution under sirolimus medication. Antenatal follow-up of cervical LM volume (red) performed by ultrasound and serum sirolimus levels measured over time by maternal blood test (blue) and fetal cordocentesis (green).

performed secondary to worsening cervical mobility, allowing considerable reduction in size. At 15 months, surgical resection of 90% of the LM was performed because of the increased mediastinal involvement. Molecular analysis of the tissue revealed a c.1624G>A (p.Glu542Lys) *PIK3CA* hot-spot mutation. Sirolimus was continued perioperatively and for 3 months after surgery and was then discontinued without issues.

The child is now 6 years and 2 months old (Fig. 3). Her growth parameters are within the normal parameters (85th percentile for head perimeter and 50th percentile for height and weight). The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) is within normal range, with a total intelligence quotient (IQ) reaching 103, a verbal IQ of 106 and a performance IQ of 100. Language development (comprehension and speaking) is normal based on the Schlichting test. Motor examination, based on Movement Assessment Battery for Children, is weaker than the average, with a manual dexterity not exceeding P37 and static–dynamic equilibrium not exceeding P25. The Beery–Buktenica Developmental Test of Visual–Motor Integration shows problems in visual–motor coordination, mainly in the visual perception (score of 62 for an average score of 100 ± 15); visual–motor integration and motor coordination are in the normal range (scores of 107 and 97, respectively, for an average score of 100 ± 15). Physiotherapeutic sessions are still ongoing (two times a week) with continuous improvement.

Discussion

This case with a long follow-up clearly demonstrates that fetal management of an LM using sirolimus, starting at 22 weeks of pregnancy, is feasible and efficient in reducing fetal LM volume. This facilitates delivery and obviates the potential indication for pregnancy termination. The efficacy of sirolimus was confirmed by the rapid size reduction of the lesion after 3 weeks of sirolimus treatment and only 1 week after achieving the maternal target sirolimus serum level of 10 ng ml^{-1} to 15 ng ml^{-1}. This target level was defined in 2015 based on the guidelines for sirolimus use in adult transplant patients[12]; however, based on studies of vascular anomalies[5–8], and on preliminary results of the European multicentric phase 3 trial (VASE trial; oral presentation at the 2020 International Society for the Study of Vascular Anomaly and manuscript in preparation, by Seront, E. et al.) on slow-flow vascular anomalies, low serum levels of sirolimus can be associated with clinical efficacy.

In 2021, after the initiation and academic discussions of our present case, a short-term sirolimus treatment (6.5 weeks) was described in a late-stage pregnancy of a fetal LM; volume reduction was observed with no major developmental defects detected during the child's first year of life[13]. Early administration of sirolimus via the mother has also been described in the management of fetal TSC rhabdomyoma. In most of the five cases, sirolimus was started in the third trimester of pregnancy[10,11].

We assessed the correlation between serum sirolimus levels in the mother and the fetus by repeated cordocentesis. Although the few clinical treatments of fetal cancer reported detectable serum level of sirolimus in the cord blood at delivery, suggesting transplacental crossing, there is no report of cordocentesis monitoring of sirolimus during pregnancy[10,14]. We showed that cordocentesis allowed detection of a correlation between sirolimus pharmacokinetics in the maternal and fetal serum levels, reflecting transplacental crossing of sirolimus. This highlights the possibility of adjusting fetal sirolimus dose by measuring maternal serum sirolimus levels; a maternal blood control performed every 5–7 d until the target range is achieved allows adaption of the daily dose of sirolimus. This pharmacokinetic correlation, yet to be confirmed by further studies, may prevent repeated cordocentesis, which can result in fetal or maternal complications, such as bleeding, fetal arrythmia, cordon occlusion, premature delivery or in utero death[15,16]. However, the variability in transplacental crossing of sirolimus among mothers is unknown.

Close follow-up imaging is necessary to assess response. Cordocentesis should be evaluated individually, especially in non-responding fetal LM. In our case, fetal serum levels at a range that would be considered subtherapeutic in a postnatal situation were shown to be highly effective in reducing the fetal LM size. The interruption of sirolimus 2 weeks before delivery was associated with a rapid increase in LM volume that required reintroduction of sirolimus shortly after birth. This suggests that, in case of voluminous and rapidly progressing LM, sirolimus should not be interrupted by the mother before delivery and should be rapidly reintroduced orally to the newborn after birth. Furthermore, this rapid postnatal evolution of the LM underscored, a posteriori, the pertinence of in utero treatment. However, we highlight the importance of close follow-up, as some LMs can spontaneously regress. Even if delivery on sirolimus is a rare event, no sirolimus-induced obstetrical complication has been reported[11,17,18].

We did not observe any intrauterine growth restriction, despite the early onset of sirolimus treatment during the pregnancy.

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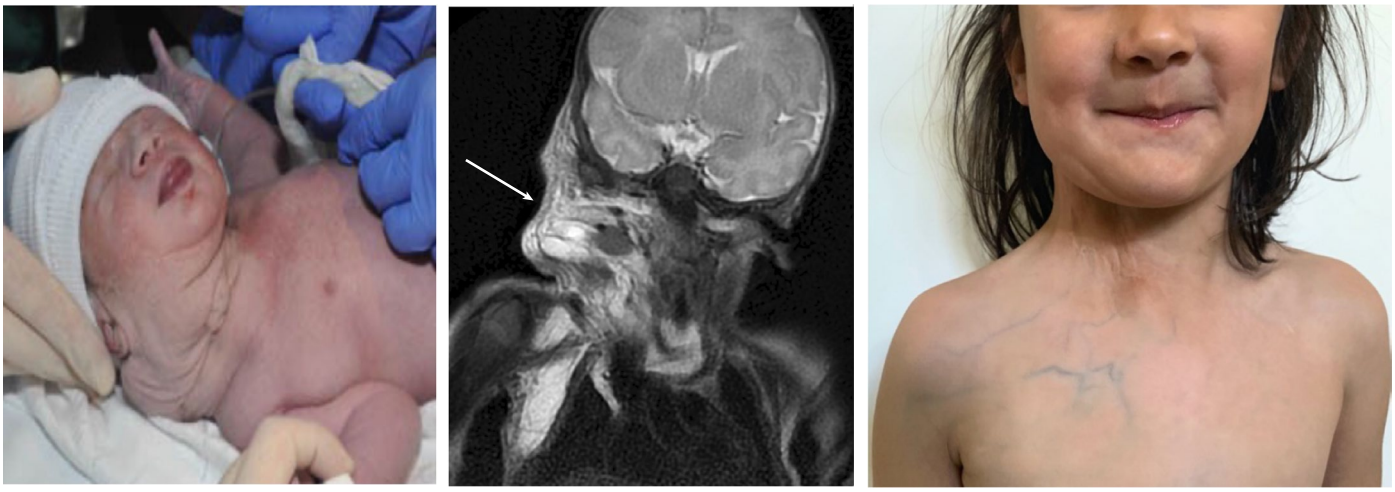

Fig. 3 | Post natal evolution. Left, LM located in the right postero-lateral cervical region at birth. Middle, MRI at birth—T2-weighted coronal view showing LM (arrows). Right, appearance at the age of 6 years.

This naturally needs confirmation in larger case series. Only a few reports have described the safety of sirolimus administered via the mother for fetal growth and development[10,19]. Sirolimus administration via the mother to treat fetal lesions in utero should be started only in an experienced multidisciplinary center, as intrauterine growth restriction was reported in a fetus treated between 28 weeks and 36 weeks of pregnancy for rhabdomyoma. The fetus was unstable before initiation of sirolimus; thus, causality is not clear[14]. Growth restriction was also observed in two sequential pregnancies of a woman who was treated with sirolimus (2 mg daily) for her blue rubber bleb nevus syndrome 12 months before and all along the pregnancies. The neonates had growth restriction at birth, but growth normalized by childhood[18].

We have not observed any delay in growth, or any trouble in cognition or intelligence, during the long follow-up of over 6 years. However, the development of coordination appears to be moderately impaired. The causality is difficult to assess, as the LM was diagnosed in the second trimester of pregnancy, and it could have impaired early intrauterine neurological development. Furthermore, the LM induced compression of superior mediastinal vessels, which may have resulted in decreased cerebral flow. Finally, the involvement of the cervicothoracic area deteriorated the static and dynamic posture, altering coordination of maturation. Long-term follow-up and physiotherapy are, therefore, required for this patient.

In conclusion, sirolimus seems to be an effective medical treatment for the management of rapidly growing in utero LMs for which fetal surgery and/or sclerotherapy are unfeasible and/or too risky. Further studies are required to ascertain the best timing to start fetal sirolimus treatment as well as the optimal dosing and long-term benefits.

Methods

Patient

In 2015, a 31-year-old woman was followed in another institution for her second pregnancy. She had no important past medical history, and the first pregnancy and delivery 2 years prior were uneventful. At gestational week 16, an extensive cervicofacial LM was detected by US. MRI at 19 weeks of gestation confirmed a large LM infiltrating the right side of the superior mediastinum, the pharynx, the jugular and carotid vessels, the parotid and the external auditory canal, with a size reaching 45 × 72 mm; upper airways appeared patent (Fig. 1). Pregnancy termination had been proposed in another center, but the parents refused it. The parents requested a second opinion in our multidisciplinary center for vascular anomalies for in utero sclerotherapy or surgery. However, both procedures were considered too risky for both the fetus and the mother.

Inclusion

We initially closely followed the LM evolution by weekly US. At gestational week 21, day 2, US showed no tracheal compression, but the volume had increased to 100 cm^3 (volume calculated by US measurement of the three largest diameters in the three planes of space). At week 22, day 3, the malformation exhibited a substantial increase in volume, reaching 240 cm^3 on US, with development of airway compression. Based on the comparative imaging tools and in front of the airway compression, it was increasingly difficult to expect a spontaneous involution of the malformation.

Ethics statement

We initiated a discussion on the experimental administration of sirolimus to the mother to treat the fetus, as we have been using sirolimus for extensive slow-flow vascular malformations since 2011 (refs. 5,6,8). The plan was submitted to, and discussed and approved by, the ethics committee of Saint-Luc University Hospital, UCLouvain. Parents received all available information and risks related to sirolimus (see details of this informed consent in the Supplementary Information). This included the FDA Pregnancy Category C of sirolimus, the absence of data concerning in utero treatment of an LM by maternal administration of sirolimus, the absence of guarantee of success as well as the importance for measuring sirolimus levels in the maternal and fetal blood in this exceptional situation. Risk of cordocentesis was explained to the parents by a specialized obstetrician team[15,16].

The risk/benefit ratio was accepted by the parents. They provided signed written consent for participation in the study and to have their child's history and photographs published. The ethics committee of Saint-Luc University Hospital, UCLouvain approved the study and its publication. There was no compensation for the parents. All data generated and analyzed during this study are included in the manuscript and related files.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

All data generated and analyzed during this study are included in the published article.

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Author contributions

E.S., A.V.D, M.V and L.M.B. conceived and designed the study. M.V. and L.M.B. obtained funds for the research. E.S., A.V.D., C.d.T., J.M.B., P.B. and L.M.B. followed the pregnancy. P.C. and D.D. analyzed the radiological data. B.L., S.S., F.V., C.P. and L.M.B. were involved in the clinical and surgical care of the child after birth. N.R. was in charge of the genetic analyses. All authors analyzed the data and contributed to writing and reviewing the manuscript. Each author approved the submitted manuscript and agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and the resolution documented in the literature.

Competing interests

The authors declare no competing interests.

Additional information

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Population characteristics	We treated a cervicofacial fetal LM with sirolimus taken orally by the mother from the 22nd week of pregnancy until 2 weeks before planned delivery and continued her management during childhood.
Recruitment	The parents requested a second opinion in our European referenced multidisciplinary Center for Vascular Anomalies as a pregnancy termination was proposed in another institution.
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