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Leflunomide exposure in pregnancy: always some uncertainty, a case report that raises questions

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Leflunomide : immunomodulator, antiproliferative action → in active rheumatoid arthritis and psoriatic arthritis

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Tériflunomide (A77 1726) : expected persistence 3.5 months after discontinuation

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⊘ **Inhibition**

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DHO-DH (dihydroorotate dehydrogenase), mitochondrial enzyme

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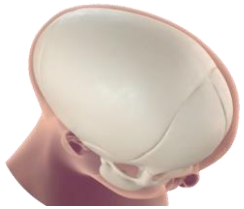
Pyrimidine synthesis → RNA/DNA synthesis → Effector T cell activation and cytokine production

Teratogenic potential of leflunomide?

Our case : 37-year-old woman with leflunomide 20 mg/d (stop15 WG, minimum exposure expected until 30WG) and abatacept (stop 22 WG). Alcohol festive consumption
37+5 WG, cesarean section for placenta praevia
Newborn (weigh 3,4 kg, height 48 cm, head circumference 35 cm), initial desaturations, axial and lower limb hypertonia, retrognatism and **scaphocephaly** by sagittal suture closure (remodeling craniectomy et 6 months)

Normal infant skull



Skull of an infant with scaphocephaly

Scaphocephaly, or sagittal craniosynostosis, is the most common form of craniosynostosis, cranial malformation resulting from premature fusion of the skull bones at the connections called sutures

Alcohol : not appear to be a major risk for craniostenosis[1-2]
Abatacept : not teratogenic in animals, few data, no risk identified

Leflunomide : here malformation similar to those found in animals
And similar malformations described in children with Miller's syndrome or postaxial acrofacial dysostosis (DHO-DH mutations) : craniofacial damage, including micrognathia and skeletal malformations

1, Fisher SC, Birth Def Res, 2024 ; 2, Van Carlen M, J Craniofac Surg 2025

Teratogenic potential of leflunomide?

Animal (rat, mice, rabbit): 

Fused or incomplete ossification, at cervical **(cranioschisis,** exencephaly) and axial level, sternebras, limbs malformations - Doses lower or equal than those used clinically

Pregnant woman: 

Overall data available do not show increase in the risk of malformations[3-8]
But to note : one case of craniosynostosis and bilateral club feet, one Pierre Robin sequence with chondrodysplasia punctate, one with unusual features of the face and neck[4-6]

Leflunomide : our case→ similar malformation to those found in animals, mechanistic hypothesis

And close anomalies described in children with Miller's syndrome or postaxial acrofacial dysostosis (with DHO-DH mutations) : craniofacial damage, including micrognathia and skeletal malformations

3 Chambers CD, Arthritis Rheum, 2010 ; 4 Cassina M, Arthritis Rheum, 2012 : 5 Berard A, Ann Rheum Dis, 2018 ;6 Henson LJ, reprod Toxicol, 2020 ; 7 Alothman R, Birth Def Res, 2023 ; 8 Princk C, Reprod Toxicol, 2024

Teratogenic potential of leflunomide?

It has been suggested that differences in enzyme (DHO-DH) kinetics may be responsible for differences in teriflunomide pharmacology between species, with animals being more sensitive to teriflunomide than humans[9]

Even though these differences and the reassuring published data

Question remains about the involvement of leflunomide or more precisely its active metabolite, teriflunomide, by inhibitory action on this enzyme DHO-DH, in the occurrence of the malformations (specially the scaphocephaly) reported in the child presented here

9, Davenport L, Neurology, 2016, *study with rat and rabbits supported by Genzyme, a Sanofi company*