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Successful pregnancy and breastfeeding in a woman with mucopolysaccharidosis type I while receiving laronidase enzyme replacement therapy

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Summary

The authors describe the first mother-infant pair to complete an on-going, prospective, open-label, Phase 4 trial (ALID 01803, NCT00418821) determining the safety of laronidase enzyme replacement therapy (ERT) in pregnant women with mucopolysaccharidosis type I (MPS I) and their breastfed infants. The mother, a 32-year-old with attenuated MPS I (Scheie syndrome), received laronidase for three years and continued treatment throughout her second pregnancy and while lactating. A healthy 2.5 kg male was delivered by elective cesarean section at 37 weeks. He was breastfed for three months. No laronidase was detected in breast milk. The infant never developed anti-laronidase IgM antibodies, never had inhibitory antibody activity in a cellular uptake assay, and always had normal urinary glycosaminoglycan (GAG) levels. No drug-related adverse events were reported. At 2.5 years of age, the boy is healthy with normal growth and development. In this first prospectively monitored mother-infant pair, laronidase during pregnancy and breastfeeding was uneventful.

Key words: Mucopolysacccharidosis type I; Laronidase; Pregnancy; Breastfeeding; Scheie syndrome.

Introduction

Mucopolysaccharidosis type I (MPS I) is a life-threatening, autosomal recessively inherited lysosomal storage disorder (LSD) that affects approximately one in 100,000 births. The disease is caused by a deficiency in lysosomal α-L-iduronidase activity, which results in the cellular accumulation of the glycosaminoglycans (GAGs) dermatan and heparan sulfate with consequent progressive multiorgan dysfunction and disability. Clinical features may include developmental delay followed by cognitive decline, coarse facial features, corneal clouding, an enlarged tongue, recurrent upper respiratory tract and ear infections, obstructive airway disease, cardiac disease, hepatosplenomegaly, skeletal deformities, short stature, joint contractures, and progressive disability. MPS I represents a disease continuum described by three main forms based on age of onset, rate of disease progression, and degree of central nervous system (CNS) involvement. The most severe form, Hurler syndrome, is characterized by early and rapidly progressive somatic and CNS involvement with death usually within the first decade in untreated patients. The most attenuated form, Scheie syndrome, presents in later childhood to adulthood with fewer and less severe somatic symptoms, such as corneal clouding, joint contractures, and valvular insufficiency. Scheie syndrome progresses slowly, is not associated with coarse facial features or CNS decline, and may have near-normal life expectancy. Hurler-Scheie syndrome, the intermediate form of MPS I, has mild to moderate CNS involvement, moderate to severe somatic involvement, variable coarsening of facial features, and a lifespan that extends into early adulthood [1].

The two main therapeutic approaches for MPS I are enzyme replacement therapy (ERT) and allogeneic hematopoietic stem cell transplantation (HSCT). Laronidase ERT (recombinant human α-L-iduronidase) was approved in 2003 to treat the non-CNS symptoms of MPS I. Laronidase is administered intravenously as a weekly infusion of 100 U/kg (0.58 mg/kg) for the life of the patient. The enzyme contains oligosaccharide chains terminating with mannose-6-phosphate residues that bind to specific cell surface receptors and enable its uptake and delivery into lysosomes. Laronidase has been shown to reduce urinary GAG levels and hepatomegaly and to improve pulmonary function, endurance, mobility, and quality of life [2, 3]. Due to its inability to cross the blood-brain-barrier, laronidase does not address CNS disease in MPS I [4]. For patients with progressive CNS involvement and cognitive decline, HSCT is considered the treatment of choice despite associated risks of morbidity and mortality. Optimal HSCT outcomes have been observed in Hurler patients who

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are under two years of age and have normal developmental quotients. When successful, early HSCT can preserve intellectual development and prolong survival [5].

Pregnancy in women with MPS I has been reported rarely. To the authors' knowledge, there are no reports in the English language literature of pregnancies in untreated women with MPS I. This may be attributable to disease rarity, high disease burden, and shortened lifespan. Case reports describe pregnancy outcomes in two women with MPS I who underwent HSCT early in life. One, a woman with Hurler syndrome, elected to terminate her pregnancy due to concerns about her health [6]. The other, a woman with Hurler-Scheie syndrome treated with HSCT at 14 months, received HSCT at three years of age and had four children later in life [7]. Another case report describes a woman with Hurler-Scheie syndrome who became pregnant while receiving laronidase as part of a clinical trial and then discontinued treatment. At 29 weeks gestation, she went into spontaneous labor and delivered a premature but healthy baby. Her clinical condition worsened rapidly during treatment withdrawal [8].

Animal studies of laronidase using over six times the human dose have not demonstrated direct or indirect harmful effects on embryonic/fetal development, parturition, or postnatal development. In the absence of adequate and well-controlled clinical trials, laronidase is recommended for use during pregnancy 'only if clearly needed'. Since it is unknown whether laronidase is excreted in human milk, 'caution' is recommended when administering laronidase to breastfeeding women [9].

As treatments for MPS I become increasingly available, more affected females are expected to survive to reproductive age and to consider having children. Without clinical data to address risk/benefit, the question remains whether to interrupt laronidase treatment during pregnancy and/or breastfeeding, which may incur a risk of disease worsening for the mother [8, 10, 11], or to continue treatment with unknown consequences for the developing fetus and breastfed infant.

Although cross-placental transfer of laronidase is expected to be minimal because of the enzyme's high molecular weight (approximately 83 kD [9]), it is unknown whether laronidase might be transferred and present a risk to the fetus. It is also unknown whether laronidase is secreted into breast milk, and whether it could harm the infant. Most patients with MPS I who receive treatment develop Immunoglobulin G (IgG) antibodies to laronidase [4], but no correlations have been demonstrated between the presence of antibodies and clinical response, as measured by the six-minute walk test (6-MWT) and forced vital capacity (FVC), or with the occurrence of allergic reactions. IgG antibodies are able to cross the placental barrier [12], but it is unknown whether trans-placental IgGs, or any potential exposure of the fetus/infant to laronidase that results in the formation of antibodies against normal endogenous enzyme, might cause an acquired enzyme deficiency.

Table 1. — *Schedule of evaluations in mother and infant.*

	Evaluation	Baseline	Within 1 month postpartum	Every 12 weeks (+/- 5 days)	End of study
Mother	Physical exam	X	X	X	X
	IgG antibody titer	X		X	X
	Inhibition of enzyme uptake	X		X	X
	Urinary GAG	X		X	X
	Breastfeeding status		X	X	X
	Laronidase in breast milk*		X	X	X
Infant	Physical examination	X	X	X	X
	IgG antibody titer	X**		X***	X***
	IgM antibody titer	X**		X***	X***
	Inhibition of enzyme uptake	X		X	X
	Urinary GAG	X		X	X
	Denver II Developmental Screening Test [17]			X	X

* Samples collected within 24 hours preceding a laronidase infusion and within 60 minutes of completing an infusion; **Obtained from umbilical cord blood at birth; ***Blood sample collection from infant is optional.
IgG and IgM antibody titers were assessed by a direct colorimetric enzyme-linked immunosorbent assay (ELISA) using specific anti-human IgG or IgM as a detector reagent. Reactivity was confirmed by radioimmunoprecipitation. Titer values are the reciprocal of the last dilution that has an absorbance value above the ELISA cut point for positivity. Enzyme cellular uptake inhibition titer was assessed using flow cytometry by determining the interference of specific antibody with intracellular incorporation of fluorescently-labeled laronidase. Urinary GAG measurements were done as previously described [2]. Laronidase activity in breast milk was measured using a 4-methylumbelliferone iduronidase enzyme activity assay with a sensitivity of 25 ng/ml.

To learn more about the effects of laronidase during pregnancy and breastfeeding, a prospective clinical trial in pregnant women with MPS I and their infants has been initiated. The authors present the clinical and obstetric history of the first mother-infant pair to complete the study.

Materials and Methods

This is an ongoing, prospective multicenter, multinational, 12- to 18-month, open-label Phase 4 trial (ALID 01803, NCT00418821) of pregnant women with a confirmed diagnosis of MPS I, who plan to receive laronidase during pregnancy and while breastfeeding (http://clinicaltrials.gov). This study was approved by the local ethics committee, conducted in accordance with the declaration of Helsinki, and performed according to Good Clinical Practice. The objectives are to determine if laronidase is present in the breast milk of postpartum women receiving laronidase, and to assess the effects of laronidase on the growth, development, and immunologic response of their breastfed infants. Mothers and their infants undergo periodic clinical, immunological and biochemical evaluations (Table 1) during the pregnancy and up to 12 months of life (if no antibodies are detected in the infant for three months), or

Table 2. — *Laboratory values in mother and infant.*

	Time point	IgG titer	Enzyme cellular uptake inhibition titer	IgM titer	Urinary GAG µg/mg creatinine (reference range for age)	Laronidase in breast milk
Mother	Baseline (delivery)	25,600	40	N/A	28 (3-36)	Negative
	3 months postpartum	51,200	20	N/A	27 (3-36)	Negative
Infant	Baseline (birth)	6,400 (in umbilical cord blood)	Negative	Negative	76 (30-300)	N/A
	3 months	Negative	Negative	Negative	194 (30-300)	N/A
	5.7 months	Negative	Negative	Negative	29 (30-300)	N/A
	8.3 months	Negative	Negative	Negative	55 (30-300)	N/A
	12 months	Negative	Negative	Negative	44 (30-300)	N/A

longer (up to 18 months). Adverse events and concomitant medications are evaluated continuously. Patients provide informed consent for themselves and their infants.

Results

The patient presented at 11 years of age with carpal tunnel syndrome requiring surgery. The rarity of carpal tunnel syndrome in children raised the suspicion for a mucopolysaccharidosis. Although the patient's urinary GAG level was normal, which may occur in patients with MPS I Scheie, genetic testing confirmed compound heterozygosity for two known MPS I mutations: p.Ala327Pro (proline for alanine substitution at amino acid 327) and c.886_887ins12 (12-base pair in-frame insertion at position 886 of iduronidase cDNA). The genotype is associated with the MPS I Scheie phenotype [13]. The patient had a history of joint stiffness and reduced mobility, which improved after initiation of ERT with laronidase (100 U/kg/week) [5] when she was 30-years-old.

The patient first became pregnant at 30 years of age. Laronidase therapy was discontinued at four weeks gestation due to insufficient safety information about the use of laronidase during pregnancy. At 11 weeks gestation, fetal data corresponded to gestational age (active fetal heart rate, active fetal movement, crown rump length, and biparietal diameter). At week 16, prenatal ultrasound showed oligohydramnios and pulmonary hypoplasia (33-52% of normal). A non-viable fetus was expelled at 17 weeks gestation. ERT with laronidase was resumed after four weeks. No change in the patient's clinical condition was observed during the interruption of laronidase treatment.

Seven months later, the patient became pregnant again. During the 37-week pregnancy, she received 28 laronidase infusions (100 U/kg/week). Treatment was interrupted during weeks 9 and 10 while the patient was deciding about participation in the clinical trial; during weeks 19 to 22 when she experienced premature labor and was treated with complete bed rest and tocolytics; and during weeks 35 to 37, when complete bed rest was advised by the treating obstetrician because of sacroiliitis, which precluded visits to the hospital for laronidase infusions. During the episode of sacroiliitis, the patient experienced reduced mobility as shown by a decline in her 6-MWT results from a peak of 275 meters to 50 meters. The patient had no radicular radiation or evidence of root compression deficits on MRI.

At 37 weeks gestation, a healthy 2.5 kg (2^{nd} to 5^{th} percentile for gestational age on the USA Centers for Disease Control and Prevention (CDC) growth charts [14]) male infant was delivered via elective caesarian section because of the mother's underlying MPS I disease. Apgar scores were 7 and 8 at one and five minutes, respectively. Physical examination of the infant at birth revealed bilateral single palmar creases, but no other dysmorphic features.

The mother resumed ERT with laronidase one week after delivery. Lactation was normal and she reported no difficulties with breastfeeding for three months. At that time, the mother stopped breastfeeding because she was prescribed an antihypertensive drug that is contraindicated during breastfeeding. Her sacroiliitis symptoms remitted four weeks after delivery, and her 6-MWT distance improved to 270 meters. She experienced a herniated disc (L4/L5), and postnatal depression documented using the Edinburgh Postnatal Depression Scale [15] (data not shown). Depression may have been influenced by the patient's spinal complication, but neither the disc herniation nor the sacroiliitis prevented the mother from caring for her child independently. Quality-of-life (QoL), monitored using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [16], worsened during the pregnancy but returned to pre-pregnancy scores within 14 weeks of delivery.

Two days before delivery, the mother was found to be seropositive for anti-laronidase IgG antibodies (titer of 25,600) (Table 2). At birth, the infant's blood in the umbilical cord tested positive for anti-laronidase IgG antibodies (titer of 6,400) and negative for anti-laronidase IgM antibodies. The infant was seronegative for anti-laronidse IgG and IgM antibodies at three months of age and at all subsequent time points during the study. A cellular enzyme uptake assay showed no inhibitory effects of antibodies in the infant throughout the study. Laronidase was not de-

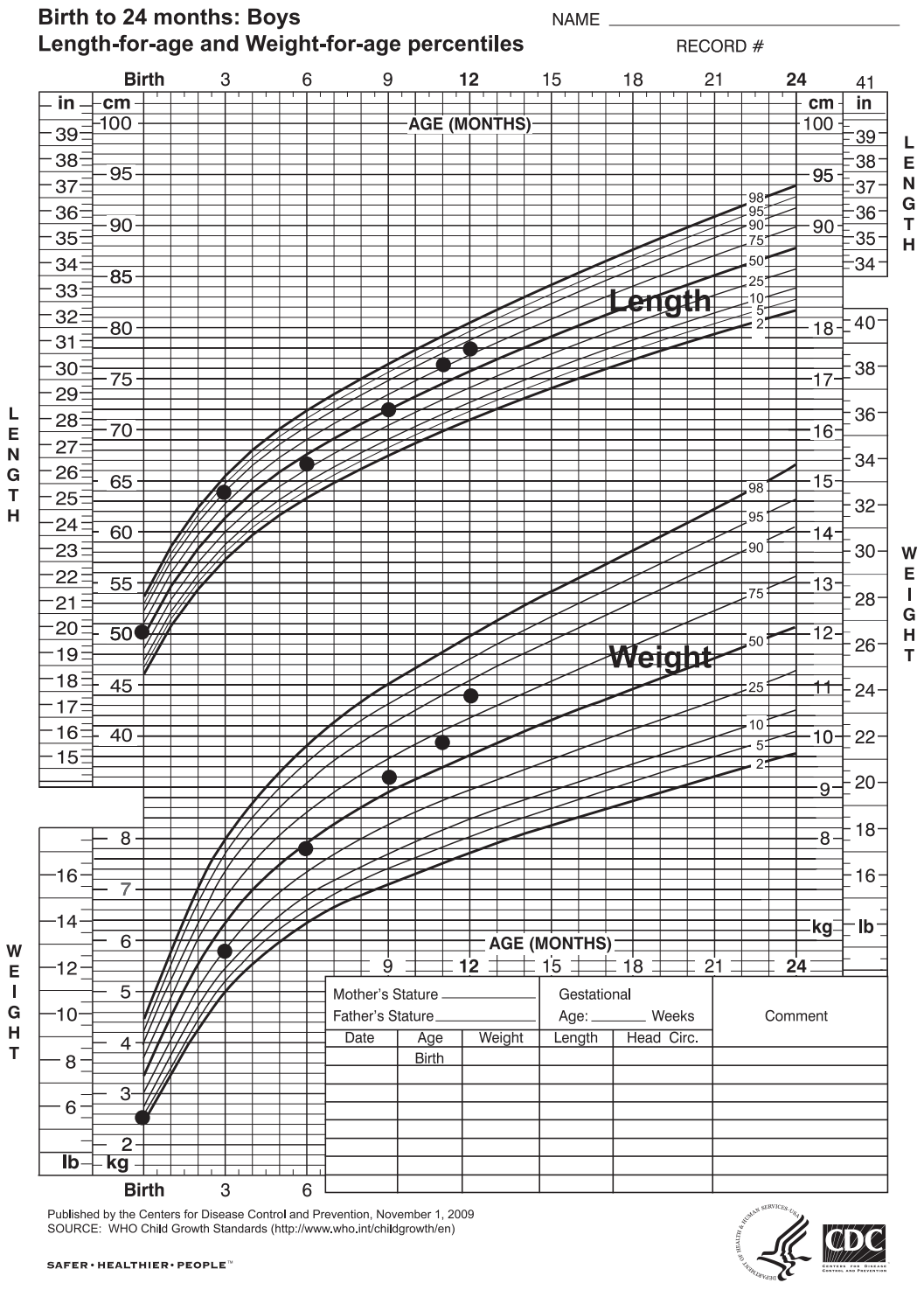

Figure 1. — Growth chart of the infant. The infant's length and weight during the evaluation period were plotted on a standard USA CDC growth chart showing the length-for-age and weight-for-age percentiles for boys from birth to 24 months of age. The chart was published by the Center for Disease Control and Prevention (www.who.int/childgrowth/en).

tectable in breast milk, before or 60 minutes after the completion of the mother's laronidase infusions at one month and three months postpartum (Table 2). Urinary GAGs were within normal range for age throughout the study for both mother and infant. No drug-related adverse events were reported.

By three months of age, the infant's weight increased to the 25th-50th percentile (Figure 1). By six months, and until the end of the study, the infant was at or above the 50th percentile for both weight and length. Denver II Development assessments [17] showed appropriate development for age. The boy, now 2.5 years old, has continued to develop normally.

Discussion

This is the first report of a successful pregnancy and lactation in a woman with MPS I Scheie while receiving ERT with laronidase. The pregnancy was uneventful and resulted in the birth of a healthy male infant. Physical examination at birth was normal with no significant congenital abnormalities. The infant was breastfed for three months, had normal growth and development throughout the 12-month study period, and continued to do well through 2.5 years of age. Laronidase was not detectable in breast milk.

Anti-laronidase IgG antibodies were detected in maternal blood and umbilical cord blood at birth, but not in the infant's blood throughout the first year of life. The infant never developed IgM antibodies to laronidase. These results are consistent with the passive trans-placental transmission of maternal IgG antibodies into the fetus and the lack of an active immunological response in the infant. The infant's normal growth, development, and urinary GAG results provide additional evidence that the mother's treatment with laronidase had no untoward effects on the infant during pregnancy and while breastfeeding.

MPS I is a progressive disorder in which early and sustained ERT may help stabilize disease and improve clinical status [4]. Treatment withdrawal may result in clinical deterioration [8, 10, 11], although the response to treatment interruption is likely to be influenced by the disease severity, rate of progression, and duration of time without therapy. A previous report involving a woman with MPS I Hurler-Scheie noted that laronidase treatment interruption for 24 months during pregnancy and postpartum resulted in hepatomegaly (liver edge 8.5 cm below the costal margin compared with a non-palpable liver edge before treatment withdrawal), reduced endurance (decrease from 340 to 259 meters on the 6-MWT), and worsening of pulmonary function (decrease in predicted FVC from 45% to 38% of normal [8]). A 13-week treatment withdrawal during the present patient's first pregnancy did not result in any apparent worsening of clinical status. The only observed deterioration during the present patient's second pregnancy (in the 6-MWT) coincided with sacroiliitis and was probably due to this spinal complication rather than MPS I-related functional deterioration. This assumption is supported by a return in 6-MWT results to pre-pregnancy values soon after delivery.

There are insufficient data to conclude that laronidase contributed to the successful outcome in this patient's second pregnancy. However, evidence from another lysosomal storage disorder, Gaucher disease, suggests that ERT with imiglucerase before and during pregnancy may be beneficial. A survey of pregnancy outcomes in women with Gaucher disease showed a statistically significant increase in the number of live births in treated mothers, fewer spontaneous abortions, and fewer complications at delivery and postpartum [18]. In Europe, women with Gaucher disease are advised to consider continuation of imiglucerase therapy before and during pregnancy and while breastfeeding, and if untreated, to initiate imiglucerase therapy before attempting to become pregnant [19]. Although data are limited for other LSDs, available evidence suggests no adverse events in infants delivered by mothers receiving ERT during pregnancy for Pompe disease [12] and Fabry disease [20-22].

In contrast to treatment for Gaucher [23] and Pompe diseases [12], where case reports showed the presence of enzyme in breast milk, laronidase was not detected in breast milk collected within 60 minutes of laronidase infusion when the pharmacokinetics of the laronidase predict peak plasma concentrations. However, peak enzyme concentration in breast milk from a woman with Pompe disease occurred two hours later than in plasma [12]. A potentially similar delay for peak laronidase concentration in breast milk may have contributed to a negative result in the present patient. Nevertheless, exogenous enzyme ingested by infants through breast milk is likely to have limited bioavailability because of its large molecular size, and enzymatic degradation, adsorption, and denaturation in the gastrointestinal tract [19].

Conclusion

The results of this case appear encouraging and may help reassure patients who may be inadvertently exposed to laronidase during pregnancy or who may consider continuing treatment throughout pregnancy and breastfeeding. Further data are required to confirm the findings presented in this report. Patients considering laronidase treatment during pregnancy should undergo an individualized risk/benefit assessment. The clinical study remains open for enrollment worldwide.

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