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Pregnancy in an Individual with Mild Smith-Lemli-Opitz Syndrome

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Smith-Lemli-Opitz syndrome (SLOS) is a recessive disorder characterized by multiple anomalies (cleft palate, postaxial polydactyly, 2/3 toe syndactyly, hypospadias, and cardiac defects), microcephaly, growth restriction, and intellectual disability. SLOS is caused by mutations in the *DHCR7* gene, which encodes 7-dehydrocholesterol reductase. Decreased enzyme activity results in low levels of plasma cholesterol and elevated cholesterol precursors, including 7-dehydrocholesterol (7DHC), which is diagnostic of SLOS. The molecular mutation detection rate is as high as 96% (1).

Here, we describe pregnancy in an individual with SLOS for the first time. Our patient is a 36-year-old referred to genetics during her second pregnancy for recurrence risk of her minor congenital anomalies. The patient's first pregnancy was achieved with clomiphene ovulation induction and intrauterine insemination with donor sperm, and resulted in a spontaneous abortion at approximately four to five weeks gestation. Her second pregnancy was achieved spontaneously. The patient has a history of a submucosal cleft palate and "fused baby teeth." Physical examination revealed a small mouth and high-pitched voice. The hands were small but without any digital anomalies. The feet were also small, and there was almost complete cutaneous syndactyly between the second and third toes bilaterally (Figure 1). The patient had short stature (height 147.7 cm, less than third percentile). Her weight was 73.0 kg, head circumference was 51.5 cm, BSA was 1.8 m², and BMI was 33.5 kg/m². She had normal intellect, with no reported history of learning disabilities, developmental delays, or behavioral abnormalities. She completed high school and college education without need for special education or tutoring.

SLOS was suspected given the patient's congenital anomalies. 7DHC plasma levels were elevated on several occasions, including postpartum time points (Table I). The patient was not treated with any drugs that cause elevated 7DHC (e.g. Aripiprazole). Molecular testing of *DHCR7* revealed the common c.964-1G>C mutation, and a novel missense variant, c.

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1083C>G (p.Phe361Leu), not reported in dbSNP. The phenylalanine residue is conserved across species. The patient's father was unavailable for testing, but the patient's mother tested positive for the c.964-1G>C mutation and negative for the c.1083C>G variant, strongly suggesting that the two *DHCR7* alterations are in *trans* and therefore likely causative of the patient's phenotype.

We measured sterols in fibroblasts grown under cholesterol replete (FBS) and cholesterol deficient (LPDS) conditions (performed at NIH, Bethesda, MD) (2). When patient skin fibroblasts were cultured in cholesterol depleted medium, the mean fraction of 7DHC to total sterols was 1.8%. These values are consistent with the mildest identified patients we have identified to date.

Cholesterol levels are typically elevated during pregnancy (3); however, this is not expected in SLOS. Due to the patient's personal and family history of hypercholesterolemia, *APOB* and *LDLR* gene analysis were conducted. The patient tested negative for the common R3500W and R3500Q *APOB* mutations. *LDLR* gene sequencing revealed two copies of the c.1773C>T polymorphism. This polymorphism results in decreased splicing efficiency of exon 12, leading to increased total and LDL-cholesterol (4). We postulate that this polymorphism has a protective effect by counteracting the SLOS-associated cholesterol synthesis defect, explaining the patient's mild phenotype.

Guidelines for management of SLOS during pregnancy do not exist due to the lack of reported cases. The diagnosis of SLOS in our patient resulted in modifications of her medical care. Changes in management included serial monitoring of cholesterol and 7DHC levels with dietary intervention to increase exogenous cholesterol and decrease the accumulation of potentially toxic cholesterol precursors. The patient met with a dietician for specific dietary management recommendations. A cholesterol loading diet, including lean meats, cheese, and eggs, was recommended beginning at approximately 29 weeks gestation. Serial fetal ultrasounds were performed due to concern for intrauterine growth restriction, heart defects, or other anomalies associated with either SLOS or toxicity due to cholesterol precursors crossing the placenta. An obstetrical anesthesia consult was also ordered due to obesity and history of cleft palate.

We followed this patient throughout her pregnancy. She underwent cesarean section at term due to breech presentation with delivery of a non-dysmorphic, healthy female. Short fallopian tubes were incidentally noted (6.5 cm versus 9.0-11.0 cm average).

SLOS is a complex condition with a variable phenotype. Although pregnancy has not been previously reported in a patient with SLOS, mild cases may be under-ascertained. Our patient had mild physical anomalies of SLOS without cognitive abnormalities. The presence of *LDLR* polymorphisms in our patient may have a modulating role in cholesterol biogenesis and as such resulted in an attenuated biochemical and clinical phenotype.

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Figure 1.
Patient's feet. Note bilateral 2/3 toe syndactyly.

Table 1

Results of biochemical testing performed during and after the patient's pregnancy.

Analyte	Gestational Age								Reference Range
	9w+3d	25w+1d	28w+2d	29w+2d	35w+1d	38w+3d	6.5w post-delivery	15m post-delivery	
Cholesterol		250	230			250	236	188	Desirable <200; borderline high 200-239 mg/dL; high $\geq$ 240
Triglycerides		293	304			412	156	215	Normal <150; borderline high 150-199 mg/dL; high >199
HDL Cholesterol		79	71			76	61	48	40-59 mg/dL
LDL Cholesterol		112	98			107	144	97	Optimal <100 mg/dL; near optimal 100-129; borderline high 130-159; high 160-189
Desmosterol		4.2	3.7			4.8	3.8		0.0-5.0 mg/L
Lathosterol		8.8	8			7.5	4.6		0.0-7.0 mg/L
Campesterol		4.8	4.5			4.1	4.2		0.0-7.0 mg/L
Sitosterol		3.7	2.1			1.9	2.7		0.0-5.0 mg/L
TSH, Sensitive		2.8							0.3-5.0 mIU/L
AM Cortisol			23						7-25 mcg/dL
PM Cortisol								1.6	2-14 mcg/dL
7-dehydrocholesterol	7.00		3.85	4.73	2.38	2.68	3.37	9.93	<2.0 ug/mL
8-dehydrocholesterol			2.46	4.08	2.47	4.37			Not detectable