Received: 26 January 2024 | Accepted: 9 April 2024

DOI: 10.1111/bjh.19480

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

LETTER TO THE EDITOR

Unplanned pregnancy in women with beta-thalassaemia treated with luspatercept

To the Editor,

Luspatercept was recently approved in order to address anaemia associated with transfusion-dependent beta-thalassaemia.[1–3]

It is contraindicated in pregnant and lactating women due to the teratogenic effects observed in preclinical animal studies. In rats, luspatercept administered at dose levels of 0, 5, 15 or 30 mg/kg on Days 3 and 10 of gestation, led to reduced uterine weight and smaller fetal body weight at all dosages. At a dosage of 30 mg/kg, the average number of fetuses and the number of live fetuses per litter were reduced. Moreover, the number of fetuses and litters with the skeletal variation 'asymmetric sternal centra' was significantly increased at 15 mg/kg. The NOAEL (no observed adverse effect level) for embryo-fetal effects in rats was 5 mg/kg, corresponding to a maternal exposure approximately three times higher than the estimated exposure at the clinical dose of 1.75 mg/kg Q3W. In rabbits, luspatercept was administered at dose levels of 0, 6, 20 and 40 mg/kg on Days 4 and 11 of gestation, with the same kinds of developmental issues, including malformations of the ribs and vertebrae and the same NOAEL, as in the rats. For this reason, an effective contraceptive regimen is recommended for the duration of the therapy and for 3 months after its discontinuation, and women of childbearing age must be guaranteed counselling with regard to planning a possible pregnancy.[4]

At the Ospedale Pediatrico Microcitemico, Cagliari (Italy), the drug is not prescribed if the patient wishes to become pregnant, or even if only considering the possibility. Contraception is recommended to all patients of childbearing age for the entire duration of luspatercept therapy, and this advice is regularly reinforced. Nevertheless, two young patients followed at that hospital became pregnant during treatment.

Patient 1 is a 27-year-old woman who has been regularly transfused since the age of 3. Chelated first with subcutaneous desferrioxamine, then with deferasirox, the patient had never presented parameters indicative of significant iron accumulation or iron-related complications. She had menarche at the age of 14, and menstruation had been regular ever since.

She started luspatercept therapy at the dosage of 1 mg/kg every 3 weeks, and the dose was increased to 1.25 mg after 3 months.

Apart from luspatercept and deferasirox at 24 mg/kg per day, the patient was being treated with vitamin D and folic acid for insufficient levels. In March 2023, she took a pregnancy test the day before the expected start day of the menstrual cycle due to nausea and asthenia, which was positive. Both iron chelation and luspatercept therapies were no longer administered. The last administration of luspatercept was 4 weeks after her last menstrual cycle. The course of the pregnancy was totally physiological, fetal growth was normal, as well as the proportions of the body and all organs assessable via ultrasound. A caesarean section was planned at 38 weeks +0 days, leading to the birth of a male weighing 3.52 kg, 51 cm in length and 35 cm in head circumference. The newborn underwent abdominal ultrasound, echocardiography, cerebral ultrasound and lab tests, which were not indicative of malformations or pathology. The patient's partner was a carrier of beta-thalassaemia. Despite the 50% risk of having an affected child, the couple had chosen not to undergo a prenatal diagnosis. The newborn resulted in being a carrier of beta-thalassaemia.

Patient 2 is a 28-year-old woman who has been regularly transfused since the age of 10 months. She had experienced menarche at 14, and her menstrual cycles were irregular. She did not consistently adhere to chelation therapy, resulting in significant iron accumulation. Severe liver overload was observed from 2012 in the absence of myocardial iron. Luspatercept therapy was started in 2021 at a dosage of 1 mg/kg every 3 weeks and transitioned to a dosage of 1.25 mg/kg after 2 cycles.

In June 2023, while undertaking luspatercept therapy, and despite having been previously advised about the need for contraception, the patient discovered her pregnancy through a positive test. Iron chelation was promptly halted, and further administrations of luspatercept were discontinued, with the last administration 4 weeks after the last menstrual cycle.

Besides luspatercept and daily deferasirox at 27 mg/kg, the patient was prescribed vitamin D and folic acid for insufficient levels. Monthly obstetric ultrasounds indicated normal embryo and fetal growth, body proportion and organ development.

The pregnancy progressed normally until 31 weeks +5 days when uterine contractions began, leading to hospitalization. A caesarean section was performed at 34 weeks

+4 days, resulting in the birth of a female weighing 2.46 kg, with a length of 45 cm and a head circumference of 32 cm that is appropriate for the gestational age. The premature birth was explained by gynaecologists by the fetopelvic disproportion that characterized the patient.

Upon birth, the infant was admitted to the neonatal intensive care unit and required respiratory assistance for a number of days. No malformations were detected via instrumental examinations. The abdominal ultrasound revealed a small peritoneal effusion and transient hepatic hyperechogenicity associated with prematurity, which rapidly resolved.

Of note, the patient had already had a first spontaneous pregnancy, in the absence of exposure to luspatercept. The offspring, weighing 2.550 kg, with a length of 47 cm and a head circumference of 33 cm, was born by caesarean section at 35 weeks +6 days that is mild preterm and appropriate for the gestational age.

The first clinical case presents a scenario that is likely to become increasingly common: a pregnancy in a woman with well-managed thalassaemia. Under the care of a multidisciplinary team, she delivers a healthy, appropriately weighted child at full term without complications.

On the contrary, the patient in the second clinical case serves as a prototype for individuals with thalassaemia for whom pregnancy should be discouraged, independent of the use of luspatercept, due to severe iron accumulation and the heightened risk of cardiac complications. It is plausible that besides the fetopelvic disproportion, the status of suboptimal iron also played a contributory role in the occurrence of preterm births.

In both cases, however, pregnancy ensued spontaneously. While the rise in spontaneous pregnancies signifies advancements in chelation therapy and the gradual mitigation of complications arising from iron overload, it also presents the possibility of unplanned pregnancies in patients who, by necessity, undergo iron chelation therapy and are therefore already exposed to a potentially teratogenic drug.[5,6] In this scenario, luspatercept thus emerges as an additional risk factor that may adversely affect embryo-fetal development and health. The absence of any apparent issues in the newborns should not diminish the importance of adhering to recommendations for effective contraception during treatment. In the event of pregnancy, it is imperative that factual information and non-directive counselling be provided, despite the limited data available on the risks associated with the use of luspatercept, a challenge commonly encountered with many pharmaceuticals. Moreover, considering the uncertainty surrounding the translation of risk data into clinical practice, a thorough discussion of all available options is warranted, including the consideration of the termination of the pregnancy if concerns regarding teratogenic effects should arise.

AUTHOR CONTRIBUTIONS

RO and EZ conceived and designed the study and wrote the original draft. All other authors were involved in data collection and reviewing the manuscript. All authors reviewed and approved the final manuscript.

FUNDING INFORMATION

N/A.

CONFLICT OF INTEREST STATEMENT

RO and SB received consultation and speaker fees from BMS. The other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

N/A.

ETHICS APPROVAL STATEMENT

N/A.

PATIENT CONSENT STATEMENT

The patients provided written consent to publish this case report.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

N/A.

CLINICAL TRIAL REGISTRATION (INCLUDING TRIAL NUMBER)

N/A.

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