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Successful pregnancy and vaginal birth in a patient with Fanconi-Bickel Syndrome – case report and literature review

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Summary

Fanconi-Bickel Syndrome (FBS) is an autosomal recessive disorder caused by mutations in SLC2A2 gene, encoding a facilitative glucose transporting membrane protein. Its phenotype can vary, and is characterized by short stature, hepatomegaly, fasting hypoglycemia, impaired glucose tolerance, hyperlipidemia, and tubular nephropathy. So far, over 100 cases in the world have been reported, and only three cases of childbearing. The authors describe a case of a 39-year-old woman affected by FBS with a spontaneous pregnancy, ending in vaginal birth at full term. In the management of a pregnant patient, possible complications that can be faced include kidney disease, urinary tract infections, gestational diabetes, polyhydramnios, cholestasis, and iatrogenic preterm birth; nevertheless, pregnancy course can be uneventful and spontaneous vaginal birth at term is feasible. This fourth report extends our knowledge about the reproductive options in this rare metabolic disease, and can be useful both for patient management and counseling.

Key words: Fanconi-Bickel Syndrome; Pregnancy; Glycogen storage disease.

Introduction

Fanconi-Bickel Syndrome (FBS) is a rare autosomal recessive disorder, discovered in 1949 [1] and recently proven to be caused by mutations in SLC2A2 gene, encoding the most important facilitative glucose transporting membrane protein GLUT2 [2, 3], which is present in hepatocytes, pancreatic beta-cells, enterocytes, and renal tubular cells [4]. In the last decade, many mutations concerning this gene have been described in patients with FBS, and none of them is particularly frequent [5]. Moreover, its phenotype can vary. So far, only three cases of pregnancy have been reported in affected patients. The authors describe a case of a 39-year-old woman affected by FBS with a spontaneous pregnancy ending in vaginal birth at full term.

Case Report

The patient was born at term after an uncomplicated pregnancy and her parents were non consanguineous and of Caucasian ancestry. FBS was diagnosed in childhood, because of impaired weight and height gain. A condition of homozygous mutation 889C-T in GLUT-2 encoding gene was detected. During her yearly follow-up, the disease was kept in a state of good compensation, with normal kidney function, no metabolic disorders, and no hepatomegaly. Only osteoporosis emerged when she was 28-years-old, treated with vitamin D and calcium supplement, along with biphosphonates; she reached 148 cm in height.

Her menarche occurred when she was 18 years-old. Subsequent menses were irregular, with phases of amenorrhea. She became spontaneously pregnant when she was 38-years-old. Diagnosis of pregnancy was established seven weeks after her last menstrual period. Her pregnancy was managed by a multidisciplinary team including an obstetrician, an expert sonographer, and a nephrologist, along with the dedicated pediatric equipe that had been following her since the diagnosis of FBS.

The patient underwent chorionic villus sampling at 11 weeks and six days of pregnancy due to maternal age, resulting in normal karyotype (46, XX). Subsequent ultrasound examinations showed no fetal abnormalities and normal Doppler-flow throughout the whole pregnancy; fetal growth was on the 30° centile, according to Paladini curves [6]. As far as renal function was concerned, mild proteinuria and glycosuria with normal creatinine concentration were present from before pregnancy. Towards term, proteinuria increased, along with polyuria and oral water intake (Table 1); blood pressure was maintained normal and lower limb edema appeared. Patient was then hospitalized at 40^{+1} weeks of pregnancy for monitoring and timing of delivery. During observation, she went into spontaneous labour at 40^{+3} weeks. Continuous electronic fetal heart rate monitoring was performed. Due to prolonged first stage of labour, augmentation was provided with amniorrhexis and then oxytocin infusion. The patient delivered an healthy female newborn, weighing 3,180 grams, that was placed skin-to-skin with the mother immediately after pediatric evaluation; umbilical artery pH was 7.26; Apgar score at one and five minutes was 9 and 10, respectively.

Puerperium was uneventful. Fluid balance and renal parameters were monitored, and urine excretion and proteinuria progressively returned to usual range. Laboratory results only showed a mild hypokalemic state (Table 1), that required oral potassium supplementation. Abdominal ultrasound showed mild hepatomegaly with initial steatosis, and a slight increase in kidney echogenicity due to mild nephropatic state. The patient was discharged on the fourth day of puerperium. Breastfeeding was interrupted soon after due to the mother's request.

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Table 1. — *Laboratory results during pregnancy and puerperium.*

Weeks of pregnancy + days	*27+1*	*34+1*	*38+2*	*39+5*	-	-	-
Days after delivery	-	-	-	-	*2*	*11*	*18*
Diuresis 24 hours (mL)	4400	5800	8000	7800	5500		3000
Proteinuria (g/L)	0.13	0.18	0.19	0.27	0.27		0.3
Proteinuria (g/24 hours)	0.57	1.04	1.52	2.12	1.51		0.9
Aspartate aminotrasnferase (U/L)	24	35	31 3	8		22	
Alanine aminotransferase (U/L)	12	16	21	27	28	19	
Creatinine (mg/dL)		0.35	0.44	0.6	0.6	0.5	0.41
Uric acid (mg/dL)		1.17	1.24	1.4	1.3		0.73
Sodium (mEq/L)		135		139	140	140	
Potassium (mEq/L)		3.5		3.8	3.3	4.2	

Discussion

FBS is a multiform disease, which can vary in phenotype. First characteristic is abnormal metabolism of glucose and galactose with fasting hypoglycemia (usually asymptomatic), impaired glucose tolerance, and hypergalactosemia [3]. Another common finding is hepatomegaly due to hepatic glycogen accumulation; it presents during infancy and seems to reduce after puberty, especially if an anti-ketogenic diet is instituted [3]. Polydipsia and polyuria, probably due to osmotic diuresis, are constant findings, usually with glycosuria, hyperaminoaciduria, moderate hyperphosphaturia, hyperuricosuria, hypercalciuria, and mild proteinuria of tubular origin [3]. Finally, severe short stature is usually present, with adult height ranging from 131.5 and 158 cm in previous reports [3].

The review by Santer *et al.* [4] reports 112 affected patients worldwide. Little is known about the way this condition can affect female fertility [7]. To date, three cases of women who became pregnant have been reported. The first one delivered with cesarean section after a pregnancy complicated by gestational diabetes mellitus treated with diet, but no other data about laboratories during her pregnancy were available [8]. The second pregnancy was complicated by kidney failure requiring daily hemodialysis, gestational cholestasis, and polyhydramnios; the patient delivered with a planned cesarean section at 34 weeks of gestation [8]. The third case is mentioned in a more recent article, but no clinical data about the pregnancy are available [7].

In the present case, no more than conservative treatment with vitamin D supplementation and yearly follow-up was needed. The patient's pregnancy was substantially uneventful, and this permitted a vaginal birth at term.

Patients with FBS usually present hyperfiltration, and often develop chronic kidney disease later in life [9]. Hypercalciuria can lead to nephrocalcinosis and nephrolitiasis; particularly in pregnancy, both physiological and mechanical changes enhance the risk of kidney stone formation [10]. Towards term, the present patient experienced an enhanced hyperfiltration, and ultrasound revealed a mild nephropatic state.

FBS patients are also at increased risk of diabetes, and sometimes this is the first symptom that leads to disease identification in neonatal period [11]. In one previous report [8], a pregnant patient with FBS had gestational diabetes, managed with diet, and subsequently continued to have impaired glucose tolerance. The present patient, despite constant glycosuria (>10 g/L), never showed hyperglycemia, and her HbA1c at term was 30 mmol/mol. She also never experienced urinary tract infections nor asymptomatic bacteriuria, that are usually promoted by glycosuria [9]. Another pregnancy complication that has been reported in a previous case is polyhydramnios [9]; this finding can be linked to a hyperglicemic state, although the mechanism behind it is still unclear [12], but the patient described had no gestational diabetes. Amniotic fluid index was normal in our patient (13 at term).

Pregnant patients with FBS can also develop cholestasis of pregnancy, as suggested in a previous report [9]. Although the cause of ICP is unknown, genetic, hormonal, and environmental factors are likely involved [13]. In FBS patients, the condition is probably related to glycogen accumulation in the liver. In the present patient, serum bile acid concentrations and liver function were normal.

Conclusion

In following a pregnant patient with FBS, a multidisciplinary team should be involved, and a close surveillance should be maintained, for early detection of complications such as worsening renal function, nephrolitiasis, gestational diabetes, urinary tract infections, polyhydramnios, and cholestasis. The degree of the disease's manifestations can be variable, unpredictable, and not necessarily complicated.

For proper counseling and follow-up, further data on FBS pregnant patient are needed, although this appears to be limited by the rarity of the condition. However, this fourth report shows that, if a state of good compensation is achieved, vaginal birth at full term is feasible.

References

[1] Fanconi G., Bickel H.: "Chronic aminoaciduria (amino acid diabetes or nephrotic-glucosuric dwarfism) in glycogen storage and cystine disease". *Helv. Paediatr. Acta*, 1949, *4*, 359.

[2] Santer R., Schneppenheim R., Dombrowski A., Götze H., Steinmann B., Schaub J.: "Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome". *Nat. Genet.*, 1997, *17*, 324.

[3] Santer R., Schneppenheim R., Suter D., Schaub J., Steinmann B.: "Fanconi-Bickel syndrome - the original patient and his natural history, historical steps leading to the primary defect, and a review of the literature". *Eur. J. Pediatr.*, 1998, *157*, 783.

[4] Santer R., Steinmann B., Schaub J.: "Fanconi-Bickel syndrome - a congenital defect of facilitative glucose transpor". *Curr. Mol. Med.*, 2002, *2*, 213.

[5] Al-Haggar M.: "Fanconi-Bickel syndrome as an example of marked allelic heterogeneity". World J. Nephrol., 2012, *6*, 63.

[6] Paladini D., Rustico M., Viora E., Giani U., Bruzzese D., Campogrande M., Martinelli P.: "Fetal size charts for the Italian population. Normative curves of head, abdomen and long bones". *Prenat. Diagn.*, 2005, *25*, 456.

[7] von Schnakenburg C., Santer R.: "Fanconi–Bickel syndrome and fertility". *Am. J. Med. Genet.*, 2011, *155*, 2607.

[8] Pena L, Charrow J.: "Fanconi-Bickel syndrome: report of life history and successful pregnancy in an affected patient". *Am. J. Med. Genet.*, 2011, *155A*, 415.

[9] Kędzierska K., Kwiatkowski S., Torbé A., Marchelek-Myśliwiec M., Marcinkiewicz O., Bobrek-Lesiakowska K., *et al.*: "Successful pregnancy in the patient with Fanconi-Bickel syndrome undergoing daily hemodialysis". *Am. J. Med. Genet.*, 2011, *155A*, 2028.

[10] Semins M.J., Matlaga B.R.: "Kidney stones during pregnancy". *Nat. Rev. Urol.*, 2014, *11*, 163.

[11] Yoo H.W., Shil Y.L., Seo E.J., Kim G.H.: "Identification of a novel mutation in the GLUT2 gene in a patient with Fanconi-Bickel syndrome presenting with neonatal diabetes mellitus and galactosaemia". *Eur. J. Pediatr.*, 2002, *161*, 351.

[12] Dashe J.D., Nathan L., McIntire D.D., Leveno K.J.: "Correlation between amniotic fluid glucose concentration and amniotic fluid volume in pregnancy complicated by diabetes". *Am. J. Obstet. Gynecol.*, 2000, *182*, 901.

[13] Arrese M, Macias RI, Briz O, Perez MJ, Marin JJ. Molecular pathogenesis of intrahepatic cholestasis of pregnancy - Expert Rev Mol Med., 2008 10:e9.

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