Dapagliflozin in a non-diabetic pregnant ckd lady an evidence for the safety of sglt2 inhibitors during pregnancy

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This is the first report of a safe use of a sodium glucose co-transporter in a pregnant lady. A heart failure female due to longstanding systemic hypertension has conceived during sacubitril/valsartan treatment. After explaining the danger of valsartan in pregnancy, the patient insisted to continue her pregnancy. Dapagliflozin was inevitably prescribed instead, after having a written consent. Pregnancy passed smoothly and the patient got a full term healthy female baby. This case should encourage attending physicians not to discontinue SGLT2 inhibitors in type 2 diabetic ladies using this medicine.

Key Words: *Dapagliflozin; Pregnant lady; Valsartan; SGLT2*

CASE SUMMARY

FZ is a 28 years old single Egyptian female housewife that was born and still living in New Valley governorate, Egypt. She was amenorrhoeic for the last 8 months before presentation. She presented to the outpatient clinic in August 2017 suffering ascites and lower limb edema for the last 2 years. Ascites was refractory to different diuretic combinations. Repeated therapeutic tapping of ascites confirmed the drained fluid as transudate. At the age of 16, she was investigated for systemic hypertension. Bilateral renal artery stenosis was discovered. In spite of right nephrectomy and left renal angioplasty, severe hypertension persisted. The patient, also, had experienced acute kidney injury following the procedure and underwent 2 sessions of hemodialysis. Since that time, she was kept on daily amlodipine 10 mg, carvedilol 25 mg twice, prazocin 2 mg twice, frusemide 40 mg twice, torsemide 20 mg twice, and omeprazole 20 mg once. On clinical examination, blood pressure was 140/80 mmHg, she had pitting edema up to the knees, congested neck veins with upper level 10 cm above the right clavicle while sitting, moderately enlarged tender liver, and moderate ascites. Apart from elevated kidney functions (Serum creatinine=1.7 mg/dL, serum urea=55 mg/dL), liver function tests, blood sugar, hemogram and serum electrolytes were unremarkable. Echo heart revealed restrictive cardiomyopathy with moderate pericardial effusion and ejection fraction 55%.

A new attempt of forced diuresis failed to control heart failure, and hence sacubitril/valsartan 24/26 mg twice daily was added. Within 2 weeks, lower limb edema almost vanished with observable improvement of abdominal girth. Echo heart and abdominal sonography performed one month after the new treatment proved disappearance of pericardial effusion and ascites. Menstruation has resumed three months later and the patient asked medical permission to get married. Two months later, pregnancy test became positive and sacubitril/valsartan was promptly discontinued. Two months later, the patient came with marked lower limb edema and respiratory distress in spite of the salt restriction and frusemide treatment. The serum creatinine was 1.6 mg/dL, urine protein/creat ratio was 0.3 gm/gm and abdominal sonography confirmed free fluid in the abdomen and a normal living fetus and adequate amniotic fluid. Dapagliflozin was introduced after discussion with the patient, her husband, and her obstetrician.

Edema and ascites improved and the patient got a healthy female baby by cesarean section at the end of the 38th week. The baby did not need special neonatal care. Serum creatinine of the baby done at age of 3 months was 0.35 mg/dL and abdominal ultrasonography is normal.

DISCUSSION

This is the first successful use of dapagliflozin over thirty weeks during pregnancy in humans. This lady is a victim bilateral renal artery fibromuscular dysplasia. This long-standing problem is the etiology of chronic kidney disease and heart failure. Although the trial of sacubutril/valsartan in patients with Heart Failure with Preserved Ejection Fraction (HFpEF) had neutral results [1], the use of this agent in women with HFpEF and decreased kidney function had a significant impact [2]. In our patient, the use of sacubitril/valsartan was associated with a prompt and near-complete resolution of her symptoms despite the long-term history of refractoriness to all other therapeutic interventions. Resumption of menstruation was another indicator of the significant improvement in the general health of this lady. The potential fetal harm of valsartan enforced us to stop sacubitril/valsartan once we became sure the patient was pregnant. Valsartan can act on the renin-angiotensin system during the second and third trimesters of pregnancy to reduce fetal renal function and increase fetal and neonatal morbidity and mortality [3]. Sodium Glucose Cotransporter 2 Inhibitors (SGLT2Is) have proved significant efficiency in reducing heart failure hospitalization [4-6]. Osmotic diuresis induced by SGLT2Is results in greater electrolyte-free water clearance. This mechanism probably causes greater fluid clearance from the interstitial fluid than from the circulation, with consequent congestion relief and minimal impact on arterial filling and organ perfusion. By reducing interstitial volume to a greater extent than blood volume [7]. In addition, SGLT2Is inhibit sodium hydrogen exchangers (NHE) on the surface of endothelial, myocardial (NHE1), and renal tubular epithelial cells (NHE3) with consequent improvement in myocardial and endothelial functions together with improved natriuresis [8,9]. Extension of the use of SGLT2Is to non-diabetic cases suffering heart failure is still evolving [10,11]. All the FDA-approved SGLT2Is are classified as pregnancy category C medications. So far, there are no adequate and well-controlled safety studies of these drugs in pregnant women. In animal studies, SGLT2Is may affect renal development and maturation [12-15] (Figure 1).

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Figure 1) Photo of the baby two months after labor

CONCLUSION

Accordingly, the use of SGLT2 Is in pregnant women was limited to situations if the potential benefits justify the risk to the fetus. The use of dapagliflozin in this lady is a real reflection of this indication.

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GUARANTOR'S STATEMENT

Professor Usama A Sharaf El Din is the guarantor of this work and, as such, had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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