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CASE REPORT

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Renal impairment in Alport syndrome pregnant woman: Case report and review of the literature

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Abstract

Pregnant women affected by Alport syndrome often struggle with worsening of renal function during pregnancy. We focused the attention on the optimal management of the kidney disease in these women in order to avoid maternal-fetal complications.

KEYWORDS

Alport syndrome, kidney disease, preeclampsia, pregnancy

1 | INTRODUCTION

Alport Syndrome (AS) is a heterogeneous genetic disease caused by defects in type IV collagen, a major component of glomerular basement membrane (GBM), causing progressive renal damage, ocular impairment, and hearing defects. AS prevalence is reported to be 1:50 000 live births[1]; moreover, it seems to affect 2% of pediatric patients on dialysis or requiring kidney transplant[2] and 5% of all patients receiving renal replacement therapy.[3]

In 65% of cases, AS is an X-linked disease arising from mutations in the COL4A5 gene on the X-chromosome (encoding the alpha 5 chains of type IV collagen), while the possibility of an autosomal recessive or autosomal dominant inheritance has been reported in 15% of cases.[4] Moreover, some cases of digenic inheritance in autosomal AS have been recently described in literature.[5]

Clinical aspects of the disease have been widely investigated in both sexes during the last 10 years.[6-9] In general, female patients affected by AS report low grade of renal impairment which may rapidly vary leading to a wide spectrum of renal outcomes.[7] However, the end-stage renal disease (ESRD) is diagnosed in 12% of women under 40 years and in 30% of female patients aged 60.[10] On the other hand, about 50% of males with X-linked AS needs dialysis or renal transplantation by age of 25 years and almost 90% develops ESRD at age <40 years. In this context, although it is possible that the inactivation of chromosome X may play a role in the disease severity for heterozygous female with AS, Yamamura et al (2017)[11] did not report any specific genotype-phenotype correlation in female X-linked AS.

With regard to kidney impairment, it may manifest with hematuria that is developed by 95% of patients and is accompanied by proteinuria in 75% of women. Proteinuria increases

the risk of ESRD; moreover, extra kidney pathology is associated with early renal failure.[12] The diagnosis of AS relies on clinical diagnostic criteria (hematuria, hearing defects, and ocular anomalies), genetic/pedigree study, and renal or skin biopsy.[13,14] Although the performance of kidney/skin biopsy may be challenging, genetic testing can today provide a definitive diagnosis in the majority of cases.[8] Moreover, genetic study represents the best solution to distinguish females who are carriers of X-linked AS from those with heterozygous COL4A3 or COL4A4 mutations. This distinction may be especially relevant in women planning a pregnancy, since in the former situation male offspring have a significant risk of ESRD during childhood and prenatal diagnosis should be suggested.[14]

Pregnancy in AS women may be risky, accelerating the progression of kidney impairment with hematuria, proteinuria, until hypertension and development of preeclampsia.

In this context, a strong consensus about the management of AS pregnant patients has not yet been established. The aim of the presented study is to report a case of successful pregnancy in a woman affected by AS and to review the recent literature about this topic.

2 | CASE REPORT

A 21-year-old woman affected by AS accessed our obstetrical first aid department at the 31st week of an unplanned pregnancy for hypertension. Patient's obstetrical history reported two previous voluntary interruption of pregnancy (VIP).

According to the patient's anamnesis, the first episode of microhematuria occurred when she was 6 years old and after puberty she developed hypoacusia. AS was previously diagnosed due to a kidney biopsy demonstrating kidney AS ultrastructural findings such as glomeruli with thickening and thinning of the basement membrane. Immunofluorescence features showed segmental/mosaic staining of the GBM and Bowman's capsule with the alpha 3 and alpha 5 chains of type IV collagen. Moreover, the complete absence of these collagen chains in the GBM as well as in the distal tubular basement membrane (dTBM) was detected by the use of immunohistochemistry.

Family history did not report any episode of proteinuria or renal failure neither AS was diagnosed in her relatives; however, her mother and grandmother experienced microhematuria and parents were consanguineous.

The patient was in therapy with angiotensin-converting enzyme (ACE) inhibitors (Enapren 2.5 mg), before the pregnancy was detected, and then, ACE inhibitor was stopped and replaced by alfa-metil-dopa 250 mg three times per die. The pregnancy had been uncomplicated until the 30th week (50th percentile fetal growth—normal umbilical and cerebral artery blood flow). Uterine arteries Doppler was reported to be normal at the 26th week of pregnancy.

When the woman accessed our department, she had high blood pressure (145/90 mm Hg) and diffuse legs edema. Routine analyses were conducted including urine test that showed proteinuria >300 mg/dL on dipstick, and 3.07 g/24-hour. Laboratory workup revealed low total serum protein (4.5 gr/dL), a significant reduction in serum albumin (1.6 mg/dL), and an increase in uric acid (6.1 mg/dL). Serum creatinine (0.7 mg/dL), creatinine clearance (101 mL/min), complete blood count, and coagulation were normal. Daily administration of low-molecular-weight heparin (LMWH) was started at the dosage of 4000 IU as thrombosis prophylaxis; moreover, spironolactone 50 mg/day was administered in order to reduce the edema. Fetal cardiotocographic test did not reveal any alteration.

Finally, fetal lung maturity was induced with betamethasone 12 mg intramuscular/daily for 2 days.

Although the therapy administration, patient's parameters rapidly worsened in the subsequent 4 days: edema and blood pressure increased (170/95 mm/Hg) and proteinuria reached nephrotic range (10.42 g/24 hour). Moreover, a decrease in hemoglobin (8.8 g/dL) and red blood cell concentration (2 860 000 mm^3) was also registered. Treatment with furosemide 20 mg intravenous twice a day was then started but did not reveal any benefit. Continuous monitoring of cardiotocography, fetal growth, umbilical and cerebral fetal Doppler were effectuated twice a day and were normal.

Due to the critical maternal condition and unfavorable obstetric conditions (0 Bishop score), the decision to perform cesarean section was taken. The newborn showed an appropriate weight for gestational age (1975 g), and the Apgar score was 9 at 1st minute and 10 at 5 minutes. The anatomo-pathological examination of placenta was normal. After delivery, maternal blood pressure and renal function recovered to normal and 24-hour proteinuria reached progressively prepregnancy levels. The patient was discharged after 6 days in good conditions.

Follow-up after 5 months showed no worsening of the renal function with proteinuria at pregnancy level and some erythrocytes in urine. The neonate was healthy.

Genetic study (Medical Genetics, University of Siena, Siena, Italy) in the pregnant woman showed a mutation associated with autosomal AS in exon 25 on COLA43 gene (mutation c.1616delGp.Glu539Lysfs*567) in 100% of analyzed molecules (next-generation sequencing on 454 Junior Roche Platform). However, the exclusion of other undetected mutations is not possible.

No genetic study has been performed on the neonate or other family's members.

3 | DISCUSSION

We report the case of a young pregnant women at 31st week affected by autosomal AS presenting with hypertension. Family history was negative for extra-renal manifestations

of AS. However, her mother and grandmother experienced microhematuria in their life. The patient developed nephrotic range proteinuria and signs of progressive renal impairment (Table 1). Due to our pharmacological and interventional approach, she delivered a healthy baby; furthermore, maternal blood pressure and renal function recovered to normal during the puerperium.

TABLE 1 Patient baseline characteristics at the access to the first aid department

Patient baseline characteristics	
Age	21 y old
Pregnancy weeks	31 wk
Family history	Microhematuria (mother and grandmother)
Therapy during pregnancy	Alfa-metil-dopa 250 mg three times per die
Access symptoms	Hypertension and legs edema
First analysis alterations	Proteinuria >300 mg/dL on dipstick and 3.07 g/24-h Total serum protein: 4.5 gr/dL Serum albumin: 1.6 mg/dL Uric acid: 6.1 mg/dL Serum creatinine: 0.7 mg/dL Creatinine clearance: 101 mL/min

Alport's syndrome is a genetic hereditary disease involving mature basement membranes of kidney, eyes and ears due to the altered production, deposition and/or function in alpha chains of type IV collagen. Few cases of pregnancy in AS patients have been described in literature so far, making difficult to manage AS pregnant women, which, in the majority of cases, show renal disease at different stages of kidney failure.[15] However, the severity of the renal impairment in AS pregnant patients seems to result from a wide complex interaction of genetic, hormonal and environmental factors.[16] In this scenario, the pregnancy impact on AS patients' renal outcomes needs to be further investigated.

Although pregnancy in AS women seems to accelerate the progression of the kidney impairment, recent evidence acquired on chronic kidney failure (CKF) underlines that pregnancy contributes to the worsening of CKF in those women who already showed advanced grade of renal disease at the initiation of the pregnancy.[17] In contrast with this last evidence, data presented in literature described also the rapid declining of the renal function even in those women with normal kidney function or low grade of renal impairment before pregnancy (Table 2).

Signs of renal failure in pregnant AS patients seem to occur during the 29-32 weeks, with reduced creatinine clearance, elevated creatinine, massive proteinuria, edema and hypertension until nephrotic syndrome, preeclampsia and/or eclampsia.[18] Moreover, AS patients showing signs of renal function deterioration are more likely to develop fetal complications such as preterm delivery[18] and/or intrauterine

TABLE 2 Literature studies evidencing renal impairment in AS pregnant women

Study	RF before pregnancy	RF during pregnancy
Omori H. et al 2004[18]	Normal	Proteinuria, reduced creatinine clearance and hypertension (third trimester)
Matsuo K. et al 2007[21]	Normal renal function with 1-2 g/24 h proteinuria	Increased creatinine, preeclampsia and acute renal failure
Zhang H. et al 2007[19]	Normal	Renal function deterioration and IUGR
Crovetto F. et al 2013[31]	Normal renal function, normal blood pressure and proteinuria <2 g/24 h	Increased proteinuria
Metha S. et al 2013[32]	Normal	Severe hypertension with 15 g/24 h proteinuria and acute kidney damage (29th week of pregnancy)
Nishizawa Y. et al 2016[22]	Normal renal function, normal blood pressure and proteinuria < 2 g/24 h	Nephrotic range proteinuria (third trimester)

Abbreviation: RF: renal function.

gestational restriction (IUGR).[19] However, the entity of proteinuria, in women with preeclampsia, is not always able to predict maternal or fetal outcomes[20]; indeed, cases of successful pregnancy with delivery of a healthy baby are also described in literature.[21-25]

With regard to the pharmacological management, the use of ACE inhibitors until conception may be considered acceptable in patients with proteinuria in order to reduce the kidney damage.[26] Once a pregnancy occurs, alfa-metil-dopa may be administered as an established therapy for arterial hypertension in pregnancy without any adverse effects on utero-placental flow or fetal well-being.[27] Moreover, low dose of acetylsalicylate (75 mg/day) may be administered to prevent preeclampsia.[28,29] When proteinuria is in the nephrotic range (3 and 3.5 g/24 h/1.73 m^2), the administration of LMWH may be indicated for thromboembolism prevention and edema may be treated with diuretics, accompanied by an accurate monitoring for oligo-hydramnios. However, evidence about the treatment of heavy edema is still insufficient to use albumin infusion, that is reported to could paradoxically increase the proteinuria.[26] According to the data reported in literature, maternal and fetal outcomes seem to be reassuring if pregnancy kidney function is maintained under control with parameters near to normal renal function, trying to avoid the development of preeclampsia and severe proteinuria. However, the presence of these symptoms in AS patients during pregnancy seems to not imply a permanent kidney damage with reversibility of the renal damage after delivery or during the puerperium months.[30]

4 | CONCLUSIONS

The management of AS during pregnancy may be challenging, and gynecologist may support AS women during their entire life.[7,8,16] However, gynecologist-obstetricians should encourage AS patients to get pregnant only after an accurate counseling about their risks. Patients counseling should include information about the possibility of developing the syndrome in the offspring and prenatal diagnosis may represent a considerable option. Pregnancy should be avoided if a significant kidney damage is already present and planned when the administration of teratogenic drugs, such as ACE inhibitors, has been stopped. To the best of our knowledge, a strict monitoring, including the study of the renal function, is advisable, especially during pregnancy, with high alert for possible maternal-fetal complications. Finally, admission to the hospital should be indicated in case of worsening of patients' conditions; similarly, delivery timing should consider maternal-fetal risk eventually linked also to prematurity.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

FP: was responsible for patient management and wrote the case presentation. FDG: prepared the manuscript, is responsible for tables design and English review. EL: contributed to the manuscript review. LMDG, GI, and SC: contributed to the research of studies suitable for the review. VLR and PP were responsible for the follow-up of the patient. All authors discussed the results and approved the final manuscript.

ETHICAL APPROVAL

The nature of the study (case report) did not require Ethics Committee approval.

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