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MATERNAL-FETAL MEDICINE

Alport syndrome and pregnancy: a case series and literature review

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Abstract

Purpose To assess pregnancy outcome in women with Alport syndrome and the impact of pregnancy on the disease progression.

Methods We describe one of the largest series of pregnancies in Alport syndrome. Seven pregnancies of six women were monitored by a multidisciplinary team of nephrologists and gynecologists. After delivery, patients were followed for at least 3 years. We compare our results with those in the literature.

Results Pregnancy course was uneventful in the patient with isolated microscopic hematuria. In the other cases, all presenting mild proteinuria at conception, some complications occurred. Proteinuria worsened during the last trimester, reaching nephrotic ranges in five out of six pregnancies and was associated with fluid overload leading to hospitalizations and early delivery. The majority of the newborns had a low birth weight. The two patients with arterial hypertension at conception and twin pregnancy developed pre-eclampsia and renal function deterioration persisted after delivery. The one with pre-pregnancy renal dysfunction reached end-stage renal disease. In the other patients, in which renal function and blood pressure were and remained normal, proteinuria improved after delivery and no signs of disease progression were recorded at last observation.

Conclusions Our observations suggest that Alport syndrome should be considered a potential risk factor for pregnancy in proteinuric patients due to the development of pre-eclampsia, renal function deterioration, and/or full-blown nephrotic syndrome that results in anasarca, slowing of fetal growth and pre-term delivery. Thus, all women with Alport syndrome should receive pre-conceptional counseling and be kept in close follow-up during pregnancy.

Keywords Alport syndrome · Pregnancy · Fetal and maternal outcome · Kidney disease progression · Proteinuria

Introduction

Alport syndrome is a rare genetic disorder characterized by an abnormality in the genes encoding the α3, α4, or α5 chains of collagen IV (*COL4A3*, *COL4A4*, and *COL4A5*) [1]. These defects lead to an inadequate structure and function at the basal membrane in different organs, including the glomeruli. Thus, the main clinical features of the disease consist of microscopic hematuria, followed by the development of proteinuria and end-stage renal disease (ESRD), together with neuro-sensorial deafness, and ocular defects [2, 3].

Three different genetic forms of Alport syndrome have been recognized so far: an X-linked type, due to a defective α5 chain, an autosomal recessive inheritance pathway, characterized by mutations of both alleles of *COL4A3* and/or *COL4A4*, and an autosomal dominant form, where the heterozygous mutation of *COL4A3* or *COL4A4* is responsible for the development of a pathological phenotype [4, 5].

The X-linked Alport syndrome represents the most frequent type [4–6]. Men affected by the X-linked form have the full-blown clinical picture of the disease and about 90% of them develop ESRD before the age of 40, depending on the mutation type they carry [7, 8]. Women that carry *COL4A5* mutation show a wide variety of phenotypes, even within the same family [9]. Unfortunately, not many data have been

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available about their clinical outcome and prognosis until recently. In the largest X-linked Alport cohort hitherto studied, dating back to 2003 [10], 28% of heterozygous females developed deafness and 75% proteinuria, which are significant risk factors for ESRD in Alport syndrome. In the same series, renal failure before the age of 40 occurred in 14% of the heterozygous women, but this percentage increased to 30–40% after 60 years.

The non-X-linked Alport syndrome forms, instead, are characterized by a comparable severity of the disease in the two genders [5]. Although the prevalence of these forms was underestimated until recently, it is now established, thanks to new sequential techniques that have enabled the identification of more patients with mutations in *COL4A3* and *COL4A4*, that they account for a consistent amount of the Alport population [5, 6].

These studies made it clear that Alport syndrome should not be regarded as a benign condition for women.

Consequently, pregnancy in patients affected by Alport syndrome should be associated with maternal and fetal risks. Unfortunately, the number of pregnancies reported in the literature is limited [11], and data about fetal and maternal outcomes in Alport syndrome are still inconclusive.

In this paper, we describe a series of seven pregnancies in six women affected by Alport syndrome. A multidisciplinary team of nephrologists and gynecologists monitored these women during the pregnancies. After delivery, the nephrological follow-up was continued for at least 3 years.

The aims of this study were: (1) to evaluate the impact of the disease on fetal and maternal outcome during pregnancy; (2) to assess the impact of pregnancy on the disease progression during the post-pregnancy follow-up; and (3) to compare our results with the other studies published on the subject.

To the best of our knowledge, our series is one of the largest and with the longest post-pregnancy follow-up hitherto reported.

Materials and methods

We collected clinical data regarding seven pregnancies of six patients affected by Alport syndrome who attended our outpatient service, led by a multidisciplinary team of nephrologists and gynecologists. Monthly clinical assessments of the mother were carried out by the same team of expert physicians, and included physical examination, blood pressure, and blood and urine tests. Complete blood cell count, renal and liver function, uric acid, serum albumin, 24 h proteinuria, and urinary sediment were recorded at the first observation (pre-pregnancy/first trimester), during advanced pregnancy (second/third trimester), after delivery, and at the end of the follow-up (≥ 3 years). Blood tests and urine analysis were all performed in the central laboratory of our hospital. Serial fetal growth scans and Doppler fetal ultrasounds were carried out every 2 weeks and more frequently during hospitalization. Hospitalization was implemented and clinical care intensified when required for mother or for fetus. Cesarean section was indicated when delivery was necessary at the 34th week of gestation or earlier.

Patients' characteristics

The main clinical characteristics at conception, during and after pregnancy, of our patients are reported in Table 1.

Our patients' age ranged from 16 to 49 years. Five patients had a genetic diagnosis of Alport syndrome. In the sixth patient, electron microscopy of kidney biopsy enabled the diagnosis. Two patients are sisters (Pt n3 and Pt n4-Table 1) and the consecutive pregnancies of one of them are described (N3–N4). Two of these pregnancies (N3 and N5) have already been reported in a previous paper [12].

At conception kidney function was normal (serum creatinine from 0.47 to 0.8 mg/dl) in all pregnancies except one (N7 serum creatinine 2.4 mg/dl). In all pregnancies, basal urinary sediment demonstrated microscopic hematuria that was associated with proteinuria in six of them (from 0.6 to 2 g/day). Before the pregnancies, all women with proteinuria were taking anti-proteinuric therapy, based on ACE inhibitors (ACE-I) and/or angiotensin receptor blockers (ARBs), that was discontinued immediately at positive pregnancy test or before conception in planned pregnancies.

Two patients had arterial hypertension well controlled with pharmacological therapy (N6–N7) and received low-dose aspirin during pregnancy. Both had twin pregnancies obtained by means of assisted reproductive techniques.

Literature comparison (Table 2)

We carried out a literature research of the papers describing pregnancies in patients affected by Alport syndrome. We only included articles in English indexed on PubMed.

Results

Maternal outcome (Table 1)

The pregnancy clinical course was completely normal and the delivery was vaginal and at term only in patient N1. In this woman, the only renal manifestation of Alport syndrome at conception was microscopic hematuria that persisted unchanged during the whole pregnancy and until the last observation, 3.2 years after delivery.

Table 1 Clinical characteristics and outcome of our seven pregnancies in patients with Alport's syndrome

Preg	Par	Pt n	AS genetic form	Age (years)	Preg type	FU (years)	Crs basal/I trim (mg/dl)	Crs III trim (mg/dl)	Crs FU (mg/dl)	uPr basal/I trim (g/24 h)	uPr III trim (g/24 h)	uPr FU (g/24 h)	BP basal/I trim	BP III trim	BP FU	Gest week/delivery type	Birth weight (g)/gender
N1	0	1	X-linked *COL4A5*	33	Single	3.2	0.6	0.8	0.7	0.1	0.18	0.0	N	N	N	38/VD	3100/F
N2	1	2	X-linked *COL4A5*+ *COL4A4*	40	Single	3.5	0.65	0.8	0.83	0.6	2.3	0.6	N	N	N	37/CS (CS for premature membrane rupture)	3210/F
N3	0	3*	X-linked *COL4A5*	19	Single	3	0.47	0.5	0.7	1.9	9.3	2	N	N	N	32/CS (labor induction and CS for critical maternal conditions)	1830/F
N4	1	3*	X-linked *COL4A5*	22	Single	3.3	0.7	0.7	0.71	2	13	1.03	N	N	N	34/CS (labor induced for worsening proteinuria; CS for previous CS)	2630/F
N5	0	4	X-linked *COL4A5*	16	Single	5.4	0.54	0.57	0.61	1.4	10.6	1.4	N	N	N	36/CS (labor induced for worsening proteinuria; CS for cervical dystocia)	2335/F

Table 1 (continued)

Preg	Par	Pt n	AS genetic form	Age (years)	Preg type	FU (years)	Crs basal/I trim (mg/dl)	Crs III trim (mg/dl)	Crs FU (mg/dl)	uPr basal/I trim (g/24 h)	uPr III trim (g/24 h)	uPr FU (g/24 h)	BP basal/I trim	BP III trim	BP FU	Gest week/delivery type	Birth weight (g)/gender
N6	0	5	N/A	49	Twin	4.5	0.8	1.12	1.2	1.6	4.5	0.9	HT 120/75	uHT 160/90	HT 130/80	33/CS (labor induction and CS performed for preeclampsia and critical mother conditions	1720/M 1480/F Dead a few hours after delivery
N7	0	6	X-linked *COL4A5*	32	Twin	5	2.4	4.4	HD; kidney Tx	1.6	5	HD; kidney Tx	HT 130/80	uHT 180/100	HT 140/85	29/CS (labor induction and CS performed for preeclampsia and critical mother conditions	1200/F 1300/M

AS Alport syndrome, *Preg* pregnancy, *Pt* patient, *n* number, *Crs* serum creatinine, *trim* trimester, *uPr* proteinuria, *BP* blood pressure, *Gest* gestational, *FU* follow-up after delivery, *N* normal, *HT* hypertension on pharmacological therapy/new onset hypertension, *uHT* uncontrolled hypertension in patient with chronic hypertension requiring therapy increase, *HD* haemodialysis, *CS* cesarean section, *VD* vaginal delivery, *Tx* transplant, *F* female, *M* male, *N/A* not available

*Consecutive pregnancies of the same patient

Table 2 Clinical characteristics and outcome of pregnancies in patients with Alport

Paper	Par[a]	Pt n	AS genetic form	Age (years)	FU	Crs basal/I trim (mg/dl)	Crs III trim (mg/dl)	Crs FU (mg/dl)	UPr basal/I trim (g/24 h)	UPr III trim (g/24 h)	UPr FU (g/24 h)	BP basal/I trim (mmHg)	BP III trim (mmHg)	BP FU (mmHg)	Gest week/delivery type	Birth weight (g)/gender
Matsuo [16]	0	1	N/A	29	6 months	1.2	6.6	HD	1–2	15	HD	HT 140/90	uHT 230/130	N/A	25/VD (labor induction for pre-eclampsia)	400/F stillbirth
Matsubara [21]	0	2*	X-linked[b]	19	2 years	0.59	0.6	0.6–0.7	1–2	2.22	1-1.5	N 110/60	N	N	39/CS (CS for fail to progress)	2862/M
Matsubara [22]	1	2*	X-linked[b]	21	2 months	0.67	0.70	0.7	1	2	1.5	N 118/62	N 123/78	N	37/CS (CS for previous CS)	2458/F
Mehta [17]	0	3	X-linked	20	24 h	0.7	1.53	1.1	1–1.4	15	0.75	N 110/70	HT 162/111	N 130/78	29/CS (labor induction for pre-eclampsia and CS for fail to induce labor)	N/A (healthy newborn)
Kitanovska [18]	0	4*	X-linked[b]	27	2 years	N	1.7	0.94	0.8	20	0.8-2	N	HT 140/80	N	30/CS (labor induction for pre-eclampsia)	880 (IUGR) baby died 7 days after for respiratory distress
	1	4*	X-linked[b]	29	6 months	1	0.81	1	2	3.5	2	N	N	N/A	39/CS	N/A (healthy newborn)

Table 2 (continued)

Paper	Par[a]	Pt n	AS genetic form	Age (years)	FU	Crs basal/I trim (mg/dl)	Crs III trim (mg/dl)	Crs FU (mg/dl)	UPr basal/I trim (g/24 h)	UPr III trim (g/24 h)	UPr FU (g/24 h)	BP basal/I trim (mmHg)	BP III trim (mmHg)	BP FU (mmHg)	Gest week/delivery type	Birth weight (g)/gender
Alessi [19]	0	5	X-linked *COL4A5*	38	22 months	N	Worsen	0.9	< 1	7	0.99	N	N	N/A	34/CS (labor induction for worsening renal function)	2165/M
	0	6	X-linked *COL4A5*	26	22 months	N	Worsen	1.48	3.26	> 7	3.21	N	uHT	N	33/VD (labor induction for pre-eclampsia)	2400/M
Yefet [11]	0	7*	AD *COL4A3*	N/A	N/A	N	N	N/A	N	N	N/A	N	N	N/A	28/VD	Stillbirth-unknown cause
	1	7*	AD *COL4A3*	20	7 years	N	N	N	N	N	N	N	N	N	At term/VD	N/A/F
	2	7*	AD *COL4A3*	27	1 year	N	N	N	N	N	N	N	N	N	At term/VD	N/A/F
	3	7*	AD *COL4A3*	28	N/A	N	N	N/A	N	N	N/A	N	N	N/A	At term/VD	N/A/F
	2	8	AD *COL4A3*	27	6 years	N/A	High	PD	> 0.5	High	PD	N/A	HT	N/A	35/VD (labor induction for pre-eclampsia)	N/A/M (healthy newborn)
	0	9*	AD[b]	20	5 years	0.6	0.9	0.75	150 mg/dl	0.5–1.5	> 0.5	N	N	N	40/VD	3500/M

Table 2 (continued)

Paper	Par[a]	Pt n	AS genetic form	Age (years)	FU	Crs basal/I trim (mg/dl)	Crs III trim (mg/dl)	Crs FU (mg/dl)	UPr basal/I trim (g/24 h)	UPr III trim (g/24 h)	UPr FU (g/24 h)	BP basal/I trim (mmHg)	BP III trim (mmHg)	BP FU (mmHg)	Gest week/delivery type	Birth weight (g)/gender
	1	9*	AD[b]	25	4 years	0.75	0.68	0.58	> 0.5	3.6	0.63	N	N	N	39/VD (labor induction for worsening proteinuria)	3100/F
	2	9*	AD[b]	29	3 years	0.58	0.7	0.8	0.63	3.95	0.6	N	N 111/71	N/A	36/VD (labor induction for worsening proteinuria)	2686/F
Nishizawa [20]	0	10	ARAs *COL4A4*	28	2 months	0.55	0.48	0.47	1.6	4.7 g/gCr	0.6 g/gCr	N 101/65	N 119/77	N	39/VD	3216/F

AS Alport syndrome, *Par* parity, *Pt* patient, *n* number, *Preg* pregnancy, *Crs* serum creatinine, *trim* trimester, *uPr* proteinuria, *BP* blood pressure, *Gest* gestational, *FU* follow-up after delivery, *HT* chronic hypertension on pharmacological therapy/new onset hypertension, *uHT* uncontrolled hypertension in patient with chronic hypertension requiring therapy increase, *N* normal, *HD* haemodialysis, *PD* peritoneal dialysis, *CS* cesarean section, *VD* vaginal delivery, *IUGR* intrauterine growth restriction, *N/A* not available, *AD* autosomic dominant Alport syndrome, *ARAs* autosomic recessive Alport syndrome, *F* female, *M* male

*Consecutive pregnancies of the same patient

[a]All pregnancies are single

[b]Not genetically confirmed

During the other pregnancies one or more complications occurred. Proteinuria, that was present at conception, worsened in all of the cases.

In pregnancy N2 proteinuria remained below 1 g/day until the third trimester when a progressive increase was documented. The patient was hospitalized; proteinuria increased to 2.3 g/day and was associated with lower limb edema onset. Renal function and arterial blood pressure remained normal. The patient delivered at 37 weeks with a cesarean section due to premature membrane rupture. After delivery, the patient restarted ARB treatment with a progressive reduction of proteinuria to the pre-pregnancy ranges, which remained stable until the last observation, 3.5 years after delivery.

In pregnancies from N3 to N7, all with mild proteinuria at conception, a striking increase of proteinuria, starting from the second trimester and reaching nephrotic levels in the third trimester (from 4.5–13 g/24 h), was documented.

Nephrotic range proteinuria was associated with fluid overload development which required hospitalization. Early delivery with cesarean section was necessary in all patients due to worsening of proteinuria, anasarca, and/or pre-eclampsia.

In cases N3, N4, and N5, proteinuria was massive. In the two former, it caused anasarca, oligoanuria, and breathlessness that required prolonged and subsequent hospitalizations from the second trimester for albumin infusions, intravenous diuretic treatment and anticoagulation with low molecular weight heparin. In pregnancy N5, the patient had to be admitted for intravenous diuretic administration.

In these three cases, renal function and arterial blood pressure continued to be in normal ranges, but delivery was brought forward (32–36 weeks) due to the massive proteinuria, the non-responsive fluid overload, and initial drop in fetal growth. Cesarean section was performed in these three cases: in pregnancies N3 and N4 because of the mother's critical conditions which required early delivery, and in N5 because of cervical dystocia after labour induction. After delivery, patients restarted treatment with ACE-I and ARB and progressive improvement of proteinuria was achieved. At last observation after delivery, their clinical conditions were comparable to that before pregnancy.

In the other two women with high blood pressure history and twin pregnancies obtained by means of assisted reproductive techniques (N6 and N7), the nephrotic proteinuria was associated with the full-blown picture of pre-eclampsia with worsening of the pre-existing arterial hypertension and of renal function. The delivery was performed at the 33rd and 29th week, respectively, with a cesarean section.

In patient N6, the worsening of renal function was mild (serum creatinine from 0.8 to 1.12 mg/dl), but persisted after delivery in spite of the progressive improvement of proteinuria that moved back rapidly after ACE-I therapy restarted. Arterial blood pressure was well controlled with the usual therapy. At last observation, 4.5 years after delivery, serum creatinine was 1.2 mg/dl, proteinuria 0.9 g/day, and blood pressure 130/80 mmHg.

In patient N7, already affected by advanced stage of chronic kidney disease (CKD) at conception, we observed a progressive worsening in renal function during the third trimester. She was started on haemodialysis 1 month after delivery and successfully underwent living related-donor kidney transplantation 2 years later. Renal graft function was normal at the last observation 5 years after pregnancy. Arterial hypertension persisted, but was in good pharmacological control with a blood pressure of 140/85 mmHg.

Fetal outcome (Table 1)

All babies were born healthy, with the exception of a female baby that died a few hours after birth due to bilateral renal dysplasia (twin pregnancy N6).

Birth weight below 2500 g was registered in five out of eight newborns (range 1200–2335 g). This high rate of low birth weight was mainly due to pre-term delivery (gestational week 29th–36th), rather than to fetal growth restriction. In fact, a small for gestational age (< 10th percentile) was recorded only in N6 twin female affected by renal dysplasia (1480 g at the 33rd gestational week), while the weights of all the other newborns in this group were appropriate for gestational age, even though in the lower ranges of normality. The birth weight of the other three babies was 2630 (N4), 3210 (N2), and 3100 g (N1), respectively. The first one was delivered pre-term (34th week), while the two latter at term (37th and 38th week).

Review of the literature (Table 2)

We performed a Medline and PubMed research on published data about pregnancy in Alport patients, including only articles in English. We found seven papers describing seventeen pregnancies of ten patients affected by different genetic forms of Alport syndrome.

It is well established that CKD and hypertension negatively impact the pregnancy outcome in different settings [13–15], and Alport patients are not an exception. In the literature, only one case of Alport syndrome with CKD and hypertension at conception was published so far by Matsuo et al. [16] (Pt n1-Table 2). The fetal and maternal outcomes were poor, and the pregnancy course was characterized by pre-eclampsia, severe fluid overload, progression to ESRD, and pre-term delivery with intrauterine fetal growth restriction (IUGR) and stillbirth. In our series, patient N7 presented similar pre-conceptional conditions and likewise developed pre-eclampsia and ESRD. Her delivery had to be early induced and she gave birth

to low-weight but healthy newborns. Another pregnancy with an analogous outcome was described by Yefet et al. [11] (Pt n8-Table 2), but neither the pre-conceptional renal function nor the blood pressure of the patient is reported. This 27 year-old woman, a carrier of an autosomal dominant form of Alport syndrome, had microscopic hematuria and proteinuria, and was at her first pregnancy. Delivery had to be brought forward due to pre-eclampsia, but she gave birth to a healthy baby. Kidney impairment that developed during pregnancy progressed subsequently to ESRD and the patient had to be started on peritoneal dialysis.

We have not found in the literature any pregnancies in women with Alport disease with chronic arterial hypertension and without CKD. This, however, is the case of our N6 patient who started pregnancy with proteinuria and normal renal function. She developed pre-eclampsia with mild but persistent deterioration of renal function. In this case, the pre-term delivery was associated with neonatal death in one of the two twins.

No other cases of ESRD developing during or following pregnancy have been described in Alport patients other than that of our patient N7 and those described by Matsuo et al. [16] and Yefet et al. [11].

Still, in four other pregnancies, renal function deterioration occurred [17–19]. All these four patients had normal renal function and blood pressure and non-nephrotic proteinuria at conception (Pt n3–6-Table 2). During pregnancy, nephrotic range proteinuria developed and pre-eclampsia occurred in three cases (Pt n3, Pt n4 1st pregnancy, Pt n6-Table 2). Delivery was induced pre-term, from 29 to 35 week gestation, with cesarean section in three (Pt n3, 4, 5-Table 2). Pregnancy resulted in a neonatal death (Pt n4-Table 2) and in three alive babies with low birth weight at least in two. Proteinuria returned to the basal values after delivery and blood pressure was normal at last observation in all patients. Nevertheless, impaired renal function persisted in two women [17, 19] (Pt n3, 6-Table 2).

In seven other pregnancies, a variable increase of proteinuria during the last trimesters complicated the clinical courses [11, 18, 20–22]. Non-nephrotic proteinuria was the only pre-conception pathological manifestation of Alport syndrome in all these patients. In two pregnancies of a young woman [11] (Pt n9-Table 2), proteinuria reached the nephrotic range. In the last pregnancy, she was admitted with headache, blurred vision, and pitting edema of lower limbs. In both pregnancies, delivery was induced due to proteinuria worsening, but no fetal complications ensued.

In two other case reports [18, 20] (Pt n4 2nd pregnancy, Pt n10-Table 2), nephrotic syndrome developed without any significant complications for the mother and the fetus. Similarly, the maternal and fetal outcomes were good in the other three cases in which the increase of proteinuria observed during pregnancy was less severe [11, 21, 22] (Pt n9 1st pregnancy, Pt n2-Table 2).

The pregnancy course of our patients who had proteinuria as the only manifestation of Alport syndrome was comparable (N2, 3, 4, 5).

Proteinuria reached nephrotic ranges in three cases (N3–5). Strict monitoring of these patients was required due to the development of severe nephrotic syndrome and severe fluid overload. This led to the need for an intense clinical care, frequent and prolonged hospitalizations, preterm deliveries, and the birth of low-weight newborns.

In the other patient (N2), the increase of proteinuria was mild and the course of pregnancy was uneventful.

As with the above-mentioned seven cases of the literature [11, 18, 20–22], also in our patients, proteinuria returned to the basal values after delivery. Our patients were monitored for more than 3 years after pregnancy and no worsening of renal function, proteinuria, and blood pressure control were recorded.

Yefet et al. [11] stated that the course of pregnancy was without any maternal complications in four pregnancies of a young carrier of an autosomal dominant Alport disease (Pt n7-Table 2). At conception, she had only isolated microscopic hematuria. Her first pregnancy ended after 28 weeks due to stillbirth, while the fetal outcome was good in the three other pregnancies. Similarly, in our patient N1, who presented isolated microscopic hematuria, the clinical course of pregnancy was uneventful, with a full-term delivery and no sequelae in the follow-up. Another pregnancy of a patient with Alport syndrome and isolated microscopic hematuria is quoted in the article of Kitanovska et al. [18], and also in this case, the outcome of pregnancy was uneventful.

It is not easy to draw definitive conclusions based on this limited number of pregnancies, the description of which sometimes misses important data. However, all these cases clearly underline that the presence of proteinuria at conception is a risk factor for the occurrence of maternal and fetal complications in Alport pregnancies. Indeed, in the absence of other well-known risk factors (arterial hypertension and CKD), some proteinuric patients can develop pre-eclampsia and transient or persistent renal dysfunction. Some other patients may develop full-blown nephrotic syndrome leading to life-threatening clinical conditions requiring hospitalization and intense medical care. In these situations, the fetal outcome could be compromised.

Discussion

There are limited data about pregnancy outcome in Alport syndrome, and clinical markers to predict fetal and maternal outcome are lacking.

To the best of our knowledge, our series of pregnant patients affected by Alport syndrome is one of the largest described in the literature and has the longest post-pregnancy follow-up, which allows us to evaluate the disease outcome after pregnancy.

Moreover, we compared our results with the other cases already published, summarized in Table 2.

In the patient who presented isolated microscopic hematuria, the clinical course of pregnancy was uneventful, with a full-term delivery and no sequelae in the follow-up.

The development of proteinuria in Alport syndrome is a marker of chronic progression of the disease [4]. In addition, proteinuria is a well-known predictor of maternal and fetal complications of pregnancies in all kidney diseases [23].

In our patients, when proteinuria was present at conception in spite of normal renal function and blood pressure, we observed its progressive increase in the second trimester and third trimester up to nephrotic ranges without other manifestations suggestive for pre-eclampsia. These patients developed severe fluid overload that led to the necessity of an intense clinical care, frequent and prolonged hospitalizations, and pre-term delivery due to the critical condition of the mother. Therefore, all but one newborn in this group had a low birth weight. Proteinuria returned to the basal degree after delivery with reintroduction of anti-proteinuric therapy. During the follow-up after pregnancy, renal function and blood pressure continued to be in normal range.

The striking increase of proteinuria during pregnancy seems a peculiar manifestation of Alport pregnancies [17–19].

Although we do not have a clear explanation for this phenomenon, we can hypothesize that it can be attributed to the impact of the physiological glomerular hyperfiltration that develops during pregnancy [24] on a genetically defective basal membrane.

As in other kidney diseases, renal function impairment and arterial hypertension at conception emerged as negative predictors for maternal and fetal outcome in pregnancies of patients with Alport syndrome [13–15]. This was the case of our two hypertensive patients who developed pre-eclampsia and deterioration of renal function. These complications required pre-term delivery and a neonatal death occurred in one of the two twin pregnancies. Probably, chronic arterial hypertension and pre-eclampsia contributed to the renal function deterioration in our patients. Indeed, chronic hypertension predisposes to pre-eclampsia and approximately 2% of women with pre-eclampsia experience acute renal failure, and those with history of renal disease do not recover renal function [25].

We should point out that these two patients of our series presented other pre-eclampsia risk factors such as old age, null parity, and twin pregnancy due to assisted reproductive techniques.

To sum up, our observations suggest that Alport syndrome should be considered a potential risk factor for pregnancy. The presence of arterial hypertension and kidney function impairment at conception confirmed as negative predictors for maternal and fetal outcome in this population; this appears to be backed up by the findings of other papers too.

Based on our series and the published cases, in the presence of proteinuria at conception, the clinical course of pregnancy can be severely complicated. As a matter of fact, some case reports underline the fact that renal function deterioration and pre-eclampsia development may occur when non-nephrotic proteinuria is present at conception, even in the absence of CKD and arterial hypertension [17–19]. In other cases, the development of severe nephrotic syndrome can worsen the pregnancy outcome.

On the other hand, a trend for patients with isolated microscopic hematuria to have an uneventful pregnancy progress stands out.

Nevertheless, in our patients with normal renal function and blood pressure at baseline, the complications that occurred during pregnancy do not seem to have worsened the mother post-pregnancy outcome. Indeed, the clinical situation of the patients at last observation was identical to the pre-conception period.

Larger patient series with a longer follow-up are warranted to draw more definitive conclusions on the long term outcome after pregnancy.

Our study has some limitations such as its retrospective nature, the low number of patients evaluated, and the heterogeneity of the population in terms of parity and age. However, we may conclude that in addition to genetic counseling, all women affected by Alport syndrome should be informed about the risks related to pregnancy in their condition and, throughout the pregnancy, mother and fetus should be regularly evaluated and carefully monitored by an expert team of nephrologists and gynecologists.

Author contribution FB data collection, data analysis, and manuscript writing/editing. BZ clinical assessment of mothers and fetus during pregnancy and patient follow-up. DG data collection. WO clinical assessment of mothers and fetus during pregnancy and patient follow-up. MG patient follow-up at diagnosis. LF paper assessment. PGM paper assessment. GM project development; clinical assessment of mothers and fetus during pregnancy and patient follow-up; data analysis and manuscript writing/editing.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the IRCCS

Ca' Granda Ospedale Maggiore Policlinico ethics committee-Milano area B- and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent Data were collected retrospectively in an anonymous database without interfering with the best clinical practice at any time during patients' follow-up. Due to the retrospective nature of the study, neither written nor verbal informed consent was necessary, according to the ethical standards of the institutional Ethics Committee.

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