“I want to become pregnant and I want to know the risks”

Dr Fawad Muhammad

ST7 Renal medicine

UHW

18/10/2019

THE RENAL ASSOCIATION
founded 1950

Clinical Practice Guideline
Pregnancy and Renal Disease

Final Version:	September 2019
Review Date:	September 2024

Case 1

- SR 22 F
- Presented with repeat episodes of **macroscopic haematuria and proteinuria in 2007**.
- A **renal biopsy was suggestive of Alport's nephropathy**.

- There is **no family history** of similar illness and no one in the family is known to have any microscopic haematuria or proteinuria.

- Investigations did not show any other positive findings and she is always known to have a normal blood pressure and **normal serum creatinine**.

- In addition **no concerns have been raised about her hearing or vision**.

- She has mild/moderate degree of proteinuria (protein/creatinine ratio between 50 – 75 mg/mmol recently) and she has been **on Enalapril since biopsy**.

- She has also been seen by the geneticist (details in her UHW notes).

2015. Adult nephrology

- HX as previously
- No auditory or visual symptoms
- Current medications: Enalapril 15mgs OD.
- Plan:
  - Routine appointment.
  - Urine PCR.
  - Enalapril current dose.
  - 6 months review.

- 2017 Pregnancy implications in her case

- 2019 Pregnancy implications in her case

- FOLLOW UP: 1 Years’ time
- WEIGHT: 66KGS
- BLOOD PRESSURE 118/66
- URINE: Nitrates +, Blood +++, Protein ++

Date	<- Time	Pre/P	(calc)	Na	K	Gluc	Creat	egfr	Urea	URR%	KT/Va	Isot	Bic
04/09/2019	15:30			141	4.6		67	95	4.4				22.0
15/08/2018	16:36			141	5.1		69	93	5.4				22.0
25/07/2017	15:19			142	4.0		60	110					
21/09/2016	15:30			140	4.4		54	125					26.0
16/12/2015	14:40			140	4.2		57	119					
17/06/2015	15:15			140	4.6		61	110					
23/02/2015	11:41			139	4.2		59	113	5.0				25.0
06/01/2014	13:45			138	3.6		52	127	3.6				
28/01/2010	11:22			139	4.2		50	126	2.6				24.0
25/09/2008	12:02			139	4.1		54	113	3.3				21.0
05/03/2008	00:00			139	4.1		50	119	3.6				
10/04/2007	00:00			141	3.8		49	118	2.3				

Date	Lab	Calc Period	Vol	Na	K	Urea	U.Crea	Cr.Cl	Pr	Pr.Excr	Pr/Cr
04/09/2019							7.1		1.4		193.00
16/08/2018							7.8		1.5		190.00
20/09/2017							3.7		1.7		460.00
06/10/2016							9.9		1.1		113.00
16/12/2015							7.4		1.8		246.00
23/02/2015							10.3		0.5		50.00
07/07/2014							18.3		1570.0		85.00
28/05/2014							10.7		1.0		93.00
22/07/2013							20.5		1530.0		74.00
10/12/2012							17.7		1820.0		100.00
07/04/2011							10.3		2080.0		200.00
24/06/2010							8.2		280.0		30.00
28/01/2010							10.1		820.0		80.00
25/09/2008							7.3		1020.0		140.00
05/03/2008							8.8		920.0		100.00
23/08/2007							11.3		1560.0		140.00
10/04/2007							11.4		4320.0		380.00
03/04/2007							13.1		3350.0		250.00

What are the risks?

Pregnancy and Chronic Kidney Disease: out comes

CKD stage (eGFR)	Early delivery (<37 weeks)	Impaired growth of baby (SGA<10%)	Worsening kidney function due to pregnancy	Dialysis within a year of pregnancy
1 (>90 ml/min)	23%	13%	8%	<1%
2 (60-90 ml/min)	50%	18%	13%	1%
3 (30-59 ml/min)	78%	19%	16%	3-10%
4-5 (<30 ml/min)	88%	50%	20%	33%

RaDaR

Archives of Gynecology and Obstetrics
June 2018, Volume 297, Issue 6, pp 1421–1431 | Cite as

Alport syndrome and pregnancy: a case series and literature review

Authors | Authors and affiliations

Francesca Brunini, Barbara Zaina, Davide Gianfreda, Wally Ossola, Marisa Giani, Luigi Fedele, Piergiorgio Messa, Gabriella Moroni

- **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 gynaecologists.

- After delivery, patients were followed for at least 3 years. We compare our results with those in the literature.

Isolated microscopic haematuria		Pregnancy course **was uneventful**	
Presenting mild proteinuria at conception		**Proteinuria worsened** during the last trimester,	**Fluid overload** leading to hospitalizations and early delivery
	Two patients with arterial hypertension at conception and twin pregnancy	Developed **pre-eclampsia**	**Renal function deterioration persisted after delivery**
	Majority of the newborns had a **low birth weight**		
	One with pre-pregnancy renal dysfunction	Reached **end-stage renal disease**.	
	Renal function and blood pressure were and remained normal	**proteinuria improved** after delivery and **no signs of disease progression** were recorded at last observation.	

- **<u>Conclusions</u>**
- Alport syndrome should be considered a **potential risk factor for pregnancy in proteinuric patients**

AWMGS (The All Wales Medical Genomics Service)

AWMGS provides specialist genetic services to individuals
and families with, or concerned about, rare genetic conditions.

The clinical and laboratory services became one in April 2019 and
together provide the medical genomics service to the population of
Wales.

Cardiff and Vale University Health Board hosts AWMGS with its home being based at the University Hospital of Wales (UHW), Heath, Cardiff.

However the service has hubs across the country with Specialist Consultant Geneticists, Doctors and Genetic Counsellors providing genetic services in all the main hospitals throughout Wales.

Who to refer?

- Anyone with a **definite family history** of Alport
- Anyone with a **fairly convincing clinical diagnosis** of Alport (although if the phenotype is strong, there is no reason why you can't **request a diagnostic genetic test yourselves**),
- Anyone with a **suggestive clinical picture** and a **reported family history** of similar issues (but only if the affected individuals are first or second degree, not distant cousins etc)

When to refer?

- Anytime is ok but if you are going to do **genetic testing yourselves, maybe best to wait till after the results come back.** Doesn't really matter though.

- If you're following someone up with **known Alport** and they are **planning a family** but would want genetic testing in pregnancy, it's good if they can be **referred before they are pregnant** so they can be given advice about their options.

Where to refer?

- All referrals should come to the **All Wales Medical Genomics Service** here at UHW – Institute of Medical Genetics (opposite maternity)

Where to find the result of any previous tests done?

- **Currently results aren't on WCP** etc but we are introducing a new LIMS system in the **New Year and that will link to WCP**. For **historical results you'll have to contact the laboratory directly.**

Where to find the family screening previously done?

- If other relatives have been seen by us **we can provide information** to you provided the **individual has given their consent**.

Local Alport syndrome service setup and help.

- I'm afraid I'm **not aware of any local services specifically for Alport** – if **you don't know of anything I guess they don't exist.**

Case 2: GP letter

- 62 M
- **Gradual decline of renal function over the past 24 months**.

- Diagnosis of **interstitial pneumonia** and on **methotrexate** 20 mg weekly.

- Methotrexate was stopped till investigations of deteriorating renal function.

- His BP is well controlled, he is not diabetic.

- He is not taking any other drugs that would impair his renal function.

- Your advice regarding his deteriorating renal function and its relevance to treatment of his lung disease with cytotoxic therapy

Past history:

- Cardiac pacemaker in situ 23.01.2018
- Wolff-Parkinson-White syndrome 23.01.2018
- Interstitial pneumonia 05.04.2017
- Chronic kidney disease stage 3 05.04.2017
- Pneumonia due to unspecified organism 27.01.2016
- Atrial fibrillation/flutter 08.08.2006

- Medication:
  - Flecainide 100 mgs bd,
  - Accrete D3 one tablet bd,
  - Alendronic Acid 70 mgs once a week,
  - Omeprazole 20 mgs od,
  - Fluoxetine 20 mgs od,
  - Verapamil 120 mgs od,
  - Apixaban 5 mgs od,
  - Bezafibrate 200 mgs od,
  - Prednisolone 10 mgs od.

Renal Medicine

- **eGFR 32 mls/min. Microscopic haematuria**.
- Renal function: **Normal 2015**.
- Past Hx of had kidney infections in the , some prostatic symptoms including nocturia
- **ACR : 4.6 mgs/mmol**
- **USS KUB: NAD.**
- **Patient concern**: Decline in his renal function may be related to his Methotrexate therapy
- **Not not aware of any connection between these two issues.**
- Plan: Renal biopsy

08/09/2006 20:36

- Urine Culture (Authorised [A])
  - Sysmex White Cells Interp <50
  - Sysmex Red Cells Interp. >50
  - Urine Culture No Growth

Mar-2013 admission under urology:

- Procedure: Flexible cystoscopy + rectal examination
- **Ultrasound scan KUB: NAD**
- **Cytology: normal.**
- PSA: normal
- Flexible cystoscopy: **NAD**
- Rectal examination: Moderate size benign feeling prostate.
- Normal investigations: **discharged**

Biopsy result:

- **MICROSCOPY:**
  - Biopsy Content: Renal cortex and medulla with 34 glomerular profiles seen in 4 levels.
- **Glomeruli:**
  - 6 (18%) are **globally sclerosed**.
  - A few of the others show **ischaemic contractions** and some **periglomerular fibrosis**.
  - **All others appear normal**, they are of normal size, show no significant mesangial thickening or hypercellularity and no segmental lesions are seen.

- **Interstitium and Tubules:**
  - There is **mild focal tubular atrophy** with associated **interstitial fibrosis** but no significant interstitial inflammation.
  - Surviving proximal tubules are of normal morphology.

- **Blood Vessels:**
  - 15 arterial profiles seen,
  - the larger show **marked elastic reduplication**;
  - smaller vessels appear normal.
  - Arterioles appear normal.

- **IMMUNOCYTOCHEMISTRY:**
  - No specific deposit of IgA, IgM or C3 identified.

- ELECTRON MICROSCOPY:
  - One glomerulus examined, normal architecture with no deposit seen in any site.
  - **GBM appear thinned (mean 209nm) but show no scalloping or fragmentation**.
  - No significant foot process fusion or endotheliosis is seen.

- SUMMARY/CONCLUSION:
  - Focal glomerular sclerosis only.
  - No specific features to determine the cause.
  - **The thin GBM may indicate an incidental thin membrane nephropathy (a collgen IV nephropathy), while this may account for the persistent haematuria it is not clear if it is responsible for the global sclerosis.**
  - The degree of renal failure is greater than would be expected from 20% global sclerosis.

Renal Medicine clinic

- The findings **do not give a clear diagnosis** that would explain his impaired renal function.

- Methotrexate or Apixaban therapy, but there was no evidence of TIN which would be the normal pattern seen in the case of drug related nephropathy.

Test Item: Creatinine

17 May 2016 10:50	*131	58	110
09 May 2016 12:45	*128	58	110
03 May 2016 10:50	*124	58	110
19 Apr 2016 10:40	*118	58	110
05 Apr 2016 00:00	*115	58	110
05 Apr 2016 00:00	*115	58	110
21 Mar 2016 00:00	*111	58	110
21 Mar 2016 00:00	*111	58	110
26 Feb 2016 11:10	106	58	110
27 Jan 2016 11:09	*128	58	110
30 Dec 2015 10:50	101	58	110
29 Dec 2015 11:30	98	58	110
28 Dec 2015 09:50	110	58	110
26 Dec 2015 11:30	*171	58	110
22 Dec 2015 10:50	*116	58	110
16 Nov 2015 10:50	*120	58	110

Currently graphing values for results within the organisation of the selected report

kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Alport syndrome: a unified classification of genetic disorders of collagen IV α345: a position paper of the Alport Syndrome Classification Working Group

Clifford E. Kashtan[1,*], Jie Ding[2], Guido Garosi[3], Laurence Heidet[4], Laura Massella[5], Koichi Nakanishi[6], Kandai Nozu[7], Alessandra Renieri[8,9], Michelle Rheault[1], Fang Wang[2], Oliver Gross[10]

DOI: https://doi.org/10.1016/j.kint.2017.12.018 | Check for updates

Table 1New classification system for Alport syndrome and related disorders			
Inheritance	**Affected gene(s)**	**Comments**	**Estimated risk of ESRD**
X-linked	*COL4A5*		100%
			Up to 25%
Autosomal Recessive	*COL4A3* or *COL4A4*		100%
Autosomal Dominant	*COL4A3* or *COL4A4*	**Includes patients previously diagnosed as TBMN/BFH**	20% or more among those with risk factors for progression, <1% in absence of risk factors
Digenic	*COL4A3*, *COL4A4,* an d *COL4A5*		20 to 100 %

Thin Glomerular Basement Membranes

Haematuria and thin GBM associated with *COL4A3*/*COL4A4* mutations	• to be called autosomal dominant Alport syndrome
Haematuria with thin glomerular basement membranes	• only when mutations in collagen IV genes cannot be identified

Histology in AS

- Light microscopy:
    - In early stages in males with X-linked Alport syndrome and in carriers:
        - Kidney biopsy is unremarkable usually
    - Later:
        - secondary glomerulosclerosis, interstitial fibrosis,

- Immunofluorescence microscopy:
    - Standard immunofluorescence shows no immune complexes.

    - Immunostaining for type IV collagen alpha chains

- Electron microscopy:
  - Early Alport or carriers of Alport
    - show diffuse thinning of GBMs.
  - In established Alport,
    - basket-weave pattern
      - irregular thin and thickened areas with splintered and irregular multi-laminated appearance of the lamina densa

GeneReviews® [Internet].

Show details

Adam MP, Ardinger HH, Pagon RA, et al., editors.
Seattle (WA): University of Washington, Seattle; 1993-2019.

Alport Syndrome

Synonyms: Familial Nephritis, Hereditary Nephritis, Thin Basement Membrane Disease, Thin Basement Membrane Nephropathy

Clifford E Kashtan, MD.

Author Information

Initial Posting: August 28, 2001; Last Update: February 21, 2019.

Clinical characteristics

- Spectrum of phenotypes
  - **Progressive renal disease with extrarenal abnormalities** → **isolated haematuria with a non-progressive** or very slowly progressive course is observed.

- Progressive sensorineural hearing loss (SNHL)
  - is usually present by late childhood or early adolescence.

- Ocular:
  - anterior lenticonus
  - maculopathy
  - and recurrent corneal erosion.

- ADAS:
  - ESRD is frequently delayed until later adulthood, S
  - NHL is relatively late in onset, and
  - ocular involvement is rare.

- Approximately two thirds of AS is X-linked (XLAS);
- Approximately 15% is autosomal recessive (ARAS),
- Approximately 20% is autosomal dominant (ADAS).

Diagnosis/testing.

- Molecular genetic testing:
  - In a proband identifying pathogenic variant(s) in *COL4A3*, *COL4A4*, or *COL4A5*

Management

Treatment of Manifestations

Manifestation/ Concern	**Treatment**	**Considerations/Other**
Renal disease	**Angiotensin-converting enzyme inhibitor** or angiotensin receptor blocker	
	Standard management for hypertension	
	Renal transplantation for ESRD	**Special considerations apply to selection of potential living related kidney donors** for individuals w/XLAS.
Hearing deficit	**Hearing aids** as needed	**Minimize exposure to loud noise**.
Vision issues	**Cataract removal**	**Protection of corneas** from minor trauma in those with recurrent corneal erosions.
Diffuse leiomyomatosis	Symptomatic leiomyomas may require surgical intervention.	

Surveillance

System/ Concern	Evaluation	Frequency
Renal	• Regular follow up by nephrologist to include • urinalysis, renal function assessment, & blood pressure determination	•**Annually** • if urine microalbumin-creatinine ratio <3 mg/mmol •**Every 6 months** •if urine microalbumin-creatinine ratio >3 mg/mmol
	For at-risk transplant recipients : monitor for development of anti-glomerular basement membrane antibody-mediated glomerulonephritis.	**Monthly for 1st 12 months post transplant**
Hearing	Audiologic evaluation starting at age 6-7 yrs	**Every 1-2 years**
Vision	Monitor for maculopathy, anterior lenticonus, corneal erosions, & cataracts.	**Starting in adolescence (in high risk group)** **Repeat every 1-2 yrs.**
Cardiac	Cardiac evaluation for aortic dilation (for males w/XLAS)	Echocardiogram follow-up interval as determined by findings & directed by cardiologist

Genetic counselling

- **In families with X-linked inheritance,**
  - Mothers
    - 50% chance of transmitting the pathogenic variant in each pregnancy
  - Sons:
    - who inherit → **develop ESRD and, in most cases, deafness**
  - Daughters:
    - who inherit → **asymptomatic haematuria** but may have **more severe renal disease**.
  - **AFFECTED MALES :**
    - will pass the pathogenic variant to all of their daughters and none of their sons.

- In families with **<u>autosomal recessive inheritance</u>**:
  - In each pregnancy
    - a 25% chance of being affected
    - a 50% chance of being a carrier
      - who may or may not be symptomatic,
    - 25% chance of being unaffected.

- In families with **autosomal dominant inheritance**:
  - In each pregnancy:
    - 50% chance of inheriting the pathogenic variant and being affected.
- In rare Alport families with digenic inheritance
  - (pathogenic variants in two or more of the *COL4A3*, *COL4A4*, and *COL4A5* genes),
  - transmission patterns may not conform to mendelian expectations.
- Molecular genetic testing for at-risk family members:
  - prenatal testing for pregnancies at increased risk, and
  - preimplantation genetic diagnosis are possible
    - if the pathogenic variant(s) in the family are known

Evaluation of relatives at risk:

- **Urinalysis** or,
- **Molecular genetic testing**
  - If the pathogenic variant(s) in the family are known

Discussion:

- Pregnancy and CKD
- Pregnancy and Alport syndrome
- Diagnosing and classifying Alport syndrome; TBMN
- Genetic testing
- Follow up
- Frequency
- Surveillance
- Genetic counselling