Reassuring pregnancy outcomes in women with mild *COL4A3-5*–related disease (Alport syndrome) and genetic type of disease can aid personalized counseling

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Individualized pre-pregnancy counseling and antenatal care for women with chronic kidney disease (CKD) require disease-specific data. Here, we investigated pregnancy outcomes and long-term kidney function in women with *COL4A3-5* related disease (Alport Syndrome, (AS)) in a large multicenter cohort. The ALPART-network (mAternaL and fetal PregnAncy outcomes of women with AlpoRT syndrome), an international collaboration of 17 centers, retrospectively investigated *COL4A3-5* related disease pregnancies after the 20th week. Outcomes were stratified per inheritance pattern (X-Linked AS (XLAS)), Autosomal Dominant AS (ADAS), or Autosomal Recessive AS (ARAS)). The influence of pregnancy on estimated glomerular filtration rate (eGFR)-slope was assessed in 192 pregnancies encompassing 116 women (121 with XLAS, 47 with ADAS, and 12 with ARAS). Median eGFR pre-pregnancy was over 90ml/min/1.73m^2. Neonatal outcomes were favorable: 100% live births, median gestational age 39.0 weeks and mean birth weight 3135 grams. Gestational hypertension occurred during 23% of pregnancies (reference: 'general' CKD G1-G2 pregnancies incidence is 4-20%) and preeclampsia in 20%. The mean eGFR declined after pregnancy but remained within normal range (over 90ml/min/1.73m^2). Pregnancy did not significantly affect eGFR-slope (pre-pregnancy β=-1.030, post-pregnancy β=-1.349). ARAS-pregnancies demonstrated less favorable outcomes (early preterm birth incidence 3/11 (27%)). ARAS was a significant independent predictor for lower birth weight and shorter duration of pregnancy, next to the classic predictors (pre-pregnancy kidney function, proteinuria, and chronic hypertension) though missing proteinuria values and the small ARAS-sample hindered analysis. This is the largest

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Received 25 February 2023; revised 22 December 2023; accepted 8 January 2024; published online 19 February 2024

study to date on AS and pregnancy with reassuring results for mild AS, though inheritance patterns could be considered in counseling next to classic risk factors. Thus, our findings support personalized reproductive care and highlight the importance of investigating kidney disease-specific pregnancy outcomes.

Kidney International (2024) **105,** 1088–1099; https://doi.org/10.1016/j.kint.2024.01.034

KEYWORDS: Alport syndrome; *COL4A3-5*–related disease; long-term kidney function; pregnancy outcomes; pre-pregnancy counseling

Lay Summary

Our study, the largest in its kind, investigated 192 pregnancies in 116 women with Alport syndrome (AS). AS is a rare genetic kidney disease and can cause pregnancy complications. Pre-pregnancy kidney function, hypertension, and urinary protein loss are risk factors for pregnancy complications in women with kidney disease in general. Data on disease-specific outcomes are needed. Together with 17 medical centers worldwide, we studied pregnancy outcomes and long-term kidney health in overall mild AS cases. Our findings are positive: babies were born after normal pregnancy duration with normal birth weight (average, 39 weeks; 3135 g). Kidney function declined after pregnancy within normal range, and pregnancy did not worsen rate of decline. However, women with a severe form of AS (autosomal recessive AS) experienced less favorable outcomes. Our results offer reassurance and help physicians tailor pregnancy care for women with AS. Considering the inheritance type of AS—alongside traditional risk factors—could help predict complications.

Chronic kidney disease (CKD) affects ≈3% of pregnancies, conveying higher risks of complications, such as preeclampsia, fetal growth restriction, and preterm birth.[1–4] Controversy exists about the exact impact of pregnancy on long-term kidney function in different CKD stages. Recent studies in the kidney transplant population[5] and advanced CKD population (stage 3–5)[6] showed a stepwise decline in estimated glomerular filtration rate (eGFR) after pregnancy, but no significant influence of pregnancy on eGFR slope. Most studies in pregnant women with CKD are based on heterogeneous cohorts, without differentiating outcomes according to cause of kidney disease.[3,7,8] Their different reported pregnancy outcomes might be explained by the modifying effect of cause. Current pre-pregnancy counseling is based on pre-pregnancy CKD category, chronic hypertension, and proteinuria.[2–4,9,10] Adding data on cause-based pregnancy outcomes could improve individualized counseling.

One of the causes lacking data on pregnancy outcomes is Alport syndrome (AS), also known as *COL4A3-5*–related disease. This is a hereditary kidney disease, caused by pathogenic variants in the collagen type IV genes (*COL4A3, COL4A4*, and *COL4A5*), leading to defect basement membranes of the ears, eyes, and kidneys. In the kidneys, defect glomerular basement membranes lead to hematuria, proteinuria, progressive loss of kidney function, and kidney failure.[11,12] Different inheritance patterns for *COL4A3-5*–related disease exist: X-linked AS (XLAS; *COL4A5* gene; incidence, 65%–80%), autosomal dominant AS (ADAS; *COL4A3* or *COL4A4* heterozygotes; 5%–20%), autosomal recessive AS (ARAS; *COL4A3* or *COL4A4* homozygotes or compound heterozygotes; 15%), or digenic.[13–15] There is growing consensus on classifying *COL4A3 or COL4A4* heterozygotes as having ADAS instead of being carriers of AS, because they may develop proteinuria, hypertension, or kidney impairment themselves as well.[12,15–17] Despite high variability in phenotype, in general, ARAS shows more severe phenotypes in women than XLAS and ADAS, with often considerable proteinuria during childhood, onset of end-stage kidney disease before 30 years of age, and more severe vascular and kidney damage. ADAS can generally be seen as the mildest form of AS, with the lowest risk of end-stage kidney disease.[11,12,14,15] Diagnosis of AS can be established by either genetic testing or kidney or skin biopsy. Because of underdiagnosis and incomplete penetrance of pathogenic variants, AS diagnosis prevalence is estimated at 1:50,000 live births, whereas the predicted population prevalence of pathogenic *COL4A5* variants is 1:2230 and heterozygous pathogenic *COL4A3* and *COL4A4* variants 1:106 in people without known kidney disease.[14,18] These numbers suggest *COL4A3-5*–related disease to be 1 of the most frequent hereditary kidney diseases.

Literature on *COL4A3-5*–related disease and pregnancy is limited to ≈30 reported cases. Reports range from having pre-pregnancy microscopic hematuria with favorable outcomes to proteinuria progressing to nephrotic range during pregnancy, hypertensive complications, and kidney replacement therapy (KRT) after pregnancy.[19–29] Given the existing literature being limited to case reports, predictors for adverse outcomes and correlation with genetic aspects could not be assessed. To better counsel patients with *COL4A3-5*–related disease who want to conceive, more information on pregnancy outcomes is needed. Therefore, the aim of this study is to report on pregnancy outcomes in women with *COL4A3-5*–related disease and to determine the influence of pregnancy on long-term kidney function.

METHODS

Study design and participants

A retrospective cohort study was conducted within the ALPART network (mAternal and foetal PregnAncy outcomes of women with AlpoRt syndrome). In 2019, the University Medical Center Utrecht established the ALPART network, an international collaboration of 17 medical centers, to investigate Alport-specific pregnancy outcomes (see Supplementary Table S1 for participants). A survey of the European Rare Kidney Disease Reference Network Workgroup

Hereditary Glomerulopathies and the international network of the research group identified ALPART collaborators. Participating sites identified pregnancies in women with *COL4A3-5*–related disease through medical file review. Eligible women included adults with ≥1 singleton pregnancy beyond 20 weeks' gestation with either (i) established genetic *COL4A3-5*–related disease diagnosis or (ii) clinically confirmed diagnosis. A clinically confirmed diagnosis was defined as (extra) renal symptoms (extrarenal: i.e., sensorineural hearing loss, ocular symptoms, such as lenticonus) and biopsy with thinning or irregular thickness of the glomerular basement membrane and/or skin biopsy with aberrant collagen α-chain staining. Extrarenal features were entered as stated in medical files, and separate audiometry results could not be retrieved. Genetic diagnosis was defined according to the American College of Medical Genetics framework for variant classification: pathogenic (class 5) or likely pathogenic (class 4) variants were considered a genetically proven diagnosis.[30] Patients with multiple variants of which ≥1 (likely) pathogenic and further variants of unknown significance were also included. Clinical and genetic diagnoses were reviewed by 2 research team members (MEG, AMvE), to establish and ascertain AS diagnosis, inheritance pattern, and inclusion. Data were collected from November 14, 2019, until December 31, 2022. This study was approved by the University Medical Center Utrecht medical ethics committee (19-238/C) and in participating centers according to local regulations.

Data collection and definitions

Data were pseudonymized and retrospectively collected by a dedicated research team member at each hospital. Data were entered using electronic case report forms into the data capture tool Castor.[31] Kidney disease characteristics, including genotype information (excluding information on base pair alterations to preserve anonymity) and maternal and neonatal pregnancy outcomes, were collected. Inheritance patterns were grouped according to the following combination of genetic and clinical criteria. XLAS: (likely) pathogenic variant in *COL4A5* gene (including variants of unknown significance/missing American College of Medical Genetics status with biopsy-proven diagnosis); ADAS: heterozygous (likely) pathogenic variant in *COL4A3 or COL4A4* gene (including variants of unknown significance/missing American College of Medical Genetics status with biopsy-proven diagnosis); and ARAS: having at least 2 homozygous/compound heterozygous maternal and paternal (likely) pathogenic variants in *COL4A3* or *COL4A4* gene. In case family segregation or pathogenicity was unavailable, severe phenotypes in combination with the compound heterozygous genotype were accepted as ARAS.

eGFR was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation without ethnicity adjustment.[32] Routinely collected serum creatinine concentrations (SCr) and date of measurement were collected at up to 9 time points: at diagnosis, 1 to 5 years pre-pregnancy, most recent pre-pregnancy, during each trimester of pregnancy, 3 months postpartum, 1 year postpartum, and most recent to date where available. Local investigators selected only representative values for data entry. In case of need for KRT, no SCr values were entered after. Chronic hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg before pregnancy,[33] use of antihypertensive medication at conception (isolated use of renin-angiotensin blockade excluded), and diastolic blood pressure >85 mm Hg at <16 weeks' gestation.[34] An extra category, "unlikely chronic hypertension," was added, for women in whom pre-pregnancy data were not retrievable (see Supplementary Methods for definition). Gestational hypertension was defined similar to chronic hypertension, only occurring at >16 weeks' gestation when no chronic hypertension previously existed. Hypertension during pregnancy was defined as gestational hypertension, only being assessed independently from the occurrence of chronic hypertension. This parameter was added because chronic hypertension status was not known for all pregnancies, and in these cases the distinction between truly new-onset (gestational) or chronic hypertension could not be determined with certainty. Proteinuria was defined as protein-to-creatinine ratio >15 mg/mmol, protein excretion rate >150 mg/24 h, protein in urine portion >140 mg/L, positive urine dipstick, use of renin-angiotensin blockade, or if stated in medical file.[35] Proteinuria during pregnancy was defined similarly, only occurring during pregnancy. Nephrotic-range proteinuria was defined as protein-to-creatinine ratio >350 mg/mmol or protein excretion rate >3500 mg/24 h.[35,36] Preeclampsia was defined by the attending physician during pregnancy, by the presence of gestational hypertension and proteinuria (>300 mg/mmol). This classification could not be uniformly defined retrospectively because of missing values. Small for gestational age was defined as birth weight below the 10th percentile on the World Health Organization Fetal Growth Charts.[37] See Supplementary Methods for additional definitions. Pregnancies after kidney transplantation were excluded. Experienced health care professionals (RS and MG) checked data rigorously and asked collaborators to provide missing values and clarifications.

Study end points

Maternal primary outcome was gestational hypertension. Fetal primary outcomes were live birth rate, duration of pregnancy, and neonatal birth weight. Secondary outcomes were long-term kidney function after pregnancy and the association of X-linked, autosomal dominant and autosomal recessive inheritance patterns and pregnancy outcomes.

Statistical analysis

As in previously published pregnancy cohorts, women were allowed to contribute ≥1 pregnancy, and analyses were performed at pregnancy level.[38] Normality of data was determined graphically by using histograms. Normally distributed continuous variables were reported as mean (SD). Skewed data were reported as median (interquartile range [IQR]). Considering the nonindependence of multiple pregnancies in 1 woman, data had a multilevel structure and were analyzed by multilevel analysis. Baseline characteristics and pregnancy outcomes were analyzed for the total cohort and stratified by inheritance pattern. Association between inheritance pattern and pregnancy outcomes was tested in multilevel prediction analysis. In this analysis, ADAS inheritance pattern was used as reference category.

The effect of pregnancy on long-term kidney function was investigated using generalized estimated equations analysis: an established method for multilevel analysis.[39] This way, eGFR trajectory could be analyzed despite varying numbers of measurements per pregnancy and clustered data from women with multiple pregnancies. As subject variable, the patient identifier was used. As within-subject variables, number of pregnancy (1, 2, 3, or 4) was used as well as measuring point of eGFR measurement (1 of 6 possible time points in data collection). The effect of time on eGFR (eGFR slope) was established by maternal age at eGFR measurement and was added to the model as a continuous covariate. Dates of eGFR measurements were divided into 4 "pregnancy intervals": interval 0 (before first pregnancy), interval 1 (between first and second

Table 1 | Baseline characteristics of the total study cohort

Variables	Total cohort (n = 192)
General characteristics	
Caucasian ethnicity	157/180 (87)
Nullipara	102/177 (58)
Age at conception, yr	29.3 (6.9)
BMI at conception, kg/m^2	22.5 (4.8)
Decennium delivery	
1970–1980	6/190 (3)
1980–1990	16/190 (8)
1990–2000	30/190 (16)
2000–2010	45/190 (24)
2010–2022	93/190 (49)
Kidney disease–specific characteristics	
Pre-pregnancy eGFR,[e] ml/min per 1.73 m^2	114 (31.5)
Pre-pregnancy serum creatinine,[e] μmol/l	64 (19)
CKD category, most recent pre-pregnancy	
G1	102/131 (78)
G2	23/131 (18)
G3[a]	4/131 (3)
G3[b]	1/131 (1)
G4	1/131 (1)
G5	0
Chronic hypertension pre-pregnancy	21/174 (12)
No	118/174 (68)
Unlikely	35/174 (20)
Pre-pregnancy proteinuria[a]	89/122 (73)
Alport-specific symptoms	
Hematuria	171/184 (93)
Extrarenal features	
Hearing loss	45/166 (27)
Ocular symptoms	30/136 (22)
Diagnosis	
Genetic testing performed	187/192 (97)
Established genetic diagnosis (LP/P)	166/187 (89)
VUS	7/187 (4)
ACMG unknown	14/187 (7)
Inclusion cohort based on	
Genetic diagnosis (LP/P)	166/192 (86)
Clinical biopsy-proven diagnosis	26/192 (14)
Kidney biopsy	25/26 (96)
Skin biopsy	1/26 (4)
XLAS[b]	121/180 (67)
ADAS[c]	47/180 (26)
ARAS[d]	12/180 (7)

Different variants per gene	*COL4A5*	*COL4A4*	*COL4A3*
Missense			
Collagenous domain	52/107 (49)	4/18 (22)	36/39 (92)
Glycine substitution	49/52	4/4	33/36
Noncollagenous domain	1/107 (1)	0	1/39 (3)
Splice site	24/107 (22)	7/18 (39)	1/39 (3)
Deletion or duplication	15/107 (14)	5/18 (28)	1/39 (3)
Premature stop codon	7/107 (7)	2/18 (11)	0
Frameshift	5/107 (5)	0	0
Other	3/107 (3)	0	0
Prenatal diagnosis			
Preimplantation genetic testing performed	3/67 (4)		
Prenatal genetic testing/ prenatal diagnosis performed	17/159 (11)		

ACMG, American College of Medical Genetics; ADAS, autosomal dominant Alport syndrome; ARAS, autosomal recessive Alport syndrome; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LP/P, likely pathogenic/pathogenic; VUS, variant of uncertain significance; XLAS, X-linked Alport syndrome.

[a]Definition of proteinuria (both pre-pregnancy and during pregnancy), if meeting ≥1 of the following criteria: protein-to-creatinine (continued) ratio >15 mg/mmol; protein excretion rate >150 mg/24 h; protein in urine portion >140 mg/L; positive dipstick proteinuria; use of renin-angiotensin blockade; or stated in the medical file.

[b]Of which 1 VUS and 11 ACMG unknown.

[c]Of which 2 VUS and 1 ACMG unknown.

[d]Of which n = 2 pregnancies with 1 variant ACMG 4: likely pathogenic and 1 variant ACMG 3: VUS; and n = 3 pregnancies with unknown segregation or pathogenicity. These pregnancies were classified ARAS because of the combination of likely compound heterozygosity and severe clinical phenotype (i.e., extrarenal features and kidney failure at young age, <50 years).

[e]Most recent before pregnancy.

Data are presented as median (IQR) unless stated otherwise. Data on genotype are presented on a pregnancy level and not on patient level. Not all baseline characteristics were available for all pregnancies. For categorical variables, incidences are shown as numerator/denominator; for continuous variables, the number of missing cases is described here: age at conception: n = 4; BMI at conception: n = 52 (27%); eGFR pre-pregnancy: n = 61 (32%); serum creatinine concentration pre-pregnancy: n = 61 (32%).

pregnancy), interval 2 (between second and third pregnancy), and interval 3 (after third pregnancy). The reference category was interval 0. The interaction term "pregnancy interval × age at eGFR measurement (time)" was added to the model to investigate whether pregnancy accelerates eGFR decline over time. An unstructured correlation matrix was used. eGFR measurements during pregnancy, after KRT, and at age <18 years were excluded.

Multilevel analyses were performed to (i) identify other factors' association with eGFR trajectory and (ii) establish the influence of pregnancy on eGFR slope, adjusted for these factors. Previously established associations with eGFR, such as pre-pregnancy kidney function, body mass index, chronic hypertension, and proteinuria, were added to analyses.[35,40–43] The dichotomous variable "after first pregnancy" appoints timing of eGFR measurement before/after first pregnancy (including pregnancy interval 1–3). Furthermore, effect of inheritance pattern and decennium of pregnancy on eGFR slope were investigated. $P < 0.05$ was considered significant. Analyses were performed using IBM SPSS Statistics version 27.0 (SPSS Inc.) and GraphPad Prism version 8.4.1 (Graph Pad Software Inc.).

Comparison to published cohorts

COL4A3-5–related disease pregnancy outcomes were compared with earlier published general CKD cohorts and the general Dutch population.[4,44,45]

RESULTS

Baseline

In total, 192 pregnancies in 116 women were included. Four pregnancies after kidney transplantation were excluded (Supplementary Figure S1). Table 1 shows baseline characteristics. Median age at pregnancy was 29.3 years (IQR, 6.9 years). Median pre-pregnancy eGFR was >90 ml/min per 1.73 m^2 (median, 114; IQR, 31.5). Median time between pregnancy and pre-pregnancy eGFR measurement was 0.62 years (IQR, 0.9 years). Most pregnancies occurred in women with pre-pregnancy CKD stage G1 to G2 (78% and 18%, respectively). Chronic hypertension occurred in 12%, and pre-pregnancy proteinuria occurred in 73%, of pregnancies (36% missing values). For most pregnancies, a genetic diagnosis had been established (86% vs. 14% clinical). In 48 of 145 (33%) of pregnancies, *COL4A3-5*–related disease was diagnosed before pregnancy. Nevertheless, in 106 of 131 (81%) pregnancies, clinical signs of AS were present pre-pregnancy already (see Supplementary Methods for definition). Most pregnancies (65%) had genetic variant(s) in *COL4A5*, 23% in *COL4A3*, and

10% in *COL4A4*. XLAS occurred in 121 pregnancies (67%), ADAS in 47 pregnancies (26%), and ARAS in 12 pregnancies (7%). Most variants in *COL4A5* and *COL4A3* were missense variants in the collagenous domain, of which were mostly glycine substitutions. In *COL4A4*, splice site variants occurred most frequently.

Complex suspected digenic inheritance

Three pregnancies showed complex suspected digenic inheritance patterns of both variants of unknown significance and (likely) pathogenic variants in *COL4A3* and *COL4A4* and were not considered for inheritance pattern analyses. For further description, see Supplementary Table S2.

Pregnancy outcomes, maternal

Table 2 shows pregnancy outcomes. Gestational hypertension occurred in 33 of 143 (23%) of pregnancies. New-onset or doubling of proteinuria occurred in 54 of 71 (76%) of pregnancies. Doubled proteinuria levels restored postpartum in 31 of 42 pregnancies (74%). Nephrotic-range proteinuria occurred in 19 of 55 (35%) of pregnancies. Quantifiable proteinuria values during all trimesters of pregnancy were missing for 60% to 70% of pregnancies. After 23 of 187 (12%) pregnancies, there was need for KRT: 17 of 187 (9%) received dialysis, and kidney transplantation was needed after 16 of 187 (9%) of pregnancies. Median start of KRT was 13.4 years (IQR, 12.2 years) after first delivery.

Table 2 | Pregnancy outcomes of the total study cohort

Variables	Total cohort (n = 192)
Maternal variables	
Hypertension during pregnancy	56/152 (37)
Gestational hypertension	33/143 (23)
Preeclampsia	37/182 (20)
Proteinuria during pregnancy	125/148 (85)
New onset or doubling of proteinuria during pregnancy	54/71 (76), missing 63%
Nephrotic-range proteinuria during pregnancy	19/55 (35), missing 71%
Induction of delivery	67/166 (40)
Maternal indication	49/57 (86)
Fetal indication	8/57 (14)
Cesarean section	40/182 (22)
Need for kidney replacement therapy after pregnancy	23/187 (12)
Dialysis	17/187 (9)
Kidney transplantation	16/187 (9)
Neonatal variables	
Live birth	190/190 (100)
Gestational age, median (IQR), wk	39.0 (2.4) (range, 26.3–42.0)
Preterm delivery	
<37 wk	32/189 (17)
<34 wk	13/189 (7)
Newborn sex, male	102/185 (55)
Birth weight, g	3135 (724)
SGA, <p10	36/184 (20)
<p3	15/184 (8)
NICU admittance within 48 h after delivery	12/172 (7)
Perinatal death (32 wk GA–7 d pp)	1/188 (0.5)

GA, gestational age; IQR, interquartile range; NICU, neonatal intensive care unit; p3, 3rd percentile; p10, 10th percentile; pp, postpartum; SGA, small for gestational age (according to the World Health Organization fetal growth calculator).[37]
Data are presented as mean (SD) and n (%) unless stated otherwise. Not all pregnancy outcomes were available for all pregnancies. For categorical variables, incidences are shown as numerator/denominator; for continuous variables, the number of missing values is described here: gestational age at delivery, n = 3; birth weight, n = 8.

Pregnancy outcomes, neonatal

Live birth rate at >20 weeks' gestational age was 100% (data for 2 pregnancies were missing). Median gestational age was 39.0 weeks (IQR, 2.4 weeks), and mean birth weight was 3135 g (SD, 724 g). A total of 67 of 166 (40%) of deliveries were induced, mostly on maternal indication (49 of 57 [86%]). Preterm birth occurred in 32 of 189 (17%), and early preterm birth (<34 weeks) occurred in 13 of 189 (7%) of pregnancies. Supplementary Table S3 shows baseline characteristics of preterm births.

Pregnancy outcomes, inheritance patterns

Supplementary Table S4 shows baseline characteristics of pregnancies stratified per inheritance pattern. Age at conception, pre-pregnancy SCr, and hearing loss differed significantly between groups. Table 3 shows pregnancy outcomes stratified per inheritance pattern. Duration of pregnancy and birth weight significantly differed between ADAS, XLAS, and ARAS pregnancies: 39.0 (SEM, 0.29), 38.5 (SEM, 0.27) and 36.0 (SEM, 0.75) weeks ($P = 0.001$); and 3751 (SEM, 303), 3176 (SEM, 82) and 2495 (SEM, 193) g ($P < 0.001$), respectively. The incidence of hypertensive disorders in pregnancy was significantly different: 22% (ADAS), 38% (XLAS), and 73% (ARAS) ($P = 0.036$). ARAS-inheritance pattern was independently associated with lower birth weight: univariable (β, –1256; SEM, 359; $P < 0.001$) and multivariable (β, –1135; SEM, 379; $P = 0.003$) when adjusted for pre-pregnancy SCr (β, 5.10; SEM, 5.25; $P = 0.331$), pre-pregnancy proteinuria (β, –153; SEM, 81; $P = 0.059$), and chronic hypertension (β, –451; SEM, 263; $P = 0.087$). Also, ARAS-inheritance pattern was independently associated with shorter duration of pregnancy: univariable (β, –2.96; SEM, 0.80; $P < 0.001$) and multivariable (β, –3.31; SEM, 1.33; $P = 0.013$), although when adjusted for pre-pregnancy proteinuria (β, –1.88; SEM, 0.42; $P < 0.001$), pre-pregnancy SCr (β, 0.01; SEM, 0.02; $P = 0.687$), and chronic hypertension (β, –0.16; SEM, 0.89; $P = 0.855$), pre-pregnancy proteinuria was a stronger predictor. Figure 1 shows adjusted marginal means of duration of pregnancy and birth weight, stratified per inheritance pattern.

Pregnancy outcomes, long-term kidney function (eGFR slope)

A total of 363 eGFR measurements were analyzed in 110 patients. Mean follow-up after first pregnancy was 4.2 years (SD, 8.88 years). Kidney function declined over time, with eGFR slope of –1.47 ml/min per 1.73 m^2 per year (SEM, 0.15 ml/min per 1.73 m^2 per year; 95% confidence interval, –1.76 to –1.18 ml/min per 1.73 m^2 per year). eGFR after first pregnancy was significantly lower than pre-pregnancy: 93.58 (SEM, 2.72) versus 99.97 (SEM, 2.20) ml/min per 1.73 m^2

Table 3 | Pregnancy outcomes, total study cohort and stratified per inheritance pattern

Variables	ADAS (N = 47)	XLAS (N = 121)	ARAS (N = 12)	*P* value
Maternal variables during pregnancy				
Hypertension during pregnancy	8/36 (22)	36/96 (38)	8/11 (73)	**0.036**
Preeclampsia	5/46 (11)	24/114 (21)	5/12 (42)	0.074
Proteinuria during pregnancy	30/37 (81)	74/89 (83)	12/12 (100)	NA
New onset or doubling of proteinuria	15/19 (79)	33/44 (75)	5/6 (83)	0.696
Nephrotic-range proteinuria during pregnancy	3/11 (27)	11/35 (31)	4/4 (100)	0.708
Induction of delivery	14/41 (34)	40/103 (39)	8/12 (67)	0.094
Cesarean section	6/46 (13)	27/113 (24)	4/12 (33)	0.563
Neonatal outcomes				
Live birth	46/46 (100)	121/121 (100)	12/12 (100)	NA
Newborn sex, male	27/45 (60)	66/116 (57)	6/12 (50)	0.072
Gestational age, mean (SEM), wk	39.0 (0.29)	38.5 (0.27)	36.0 (0.75)	**0.001**
Preterm delivery				
<37 wk	5/46 (11)	17/121 (14)	5/11 (46)	**0.017**
<34 wk	0	8/121 (7)	3/11 (27)	NA
Birth weight, mean (SEM), g	3751 (303)	3176 (82)	2495 (193)	**<0.001**
Small for gestational age, <p10	4/46 (9)	24/117 (21)	5/11 (46)	0.075
NICU admittance within 48 h after delivery	2/43 (5)	7/108 (7)	2/11 (18)	NA
Perinatal death (32 wk GA–7 d pp)	0	1/120 (1)	0	NA

ADAS, autosomal dominant Alport syndrome; ARAS, autosomal recessive Alport syndrome; GA, gestational age; NA, not applicable; NICU, neonatal intensive care unit; pp, postpartum; XLAS, X-linked Alport syndrome.
In multilevel analysis, ADAS inheritance pattern was used as reference category. Continuous variables, stratified per different inheritance pattern, are presented as marginal means (SEM). Continuous variables for the total cohort are presented as mean (SD) and number/total (percentage) unless stated otherwise. Not all pregnancy outcomes were available for all pregnancies. For categorical variables, incidences are shown as numerator/denominator; and for continuous variables, the number of missing values is described here: gestational age, n = 3; birth weight, n = 8. Bold variables are significant ($P < 0.05$).

($P = 0.004$). eGFR after second and third pregnancy was not significantly lower (97.94 [SEM, 3.18] ml/min per 1.73 m^2 [$P = 0.564$] and 99.80 [SEM, 4.96] ml/min per 1.73 m^2 [$P = 0.975$]).

Mean eGFR decline, adjusted for time, in pregnancy interval 1 was –6.40 ml/min per 1.73 m^2 (SEM, 2.25 ml/min per 1.73 m^2; 95% confidence interval, –10.80 to –1.99 ml/min per 1.73 m^2) over 1.92 years (IQR, 2.70 years). In

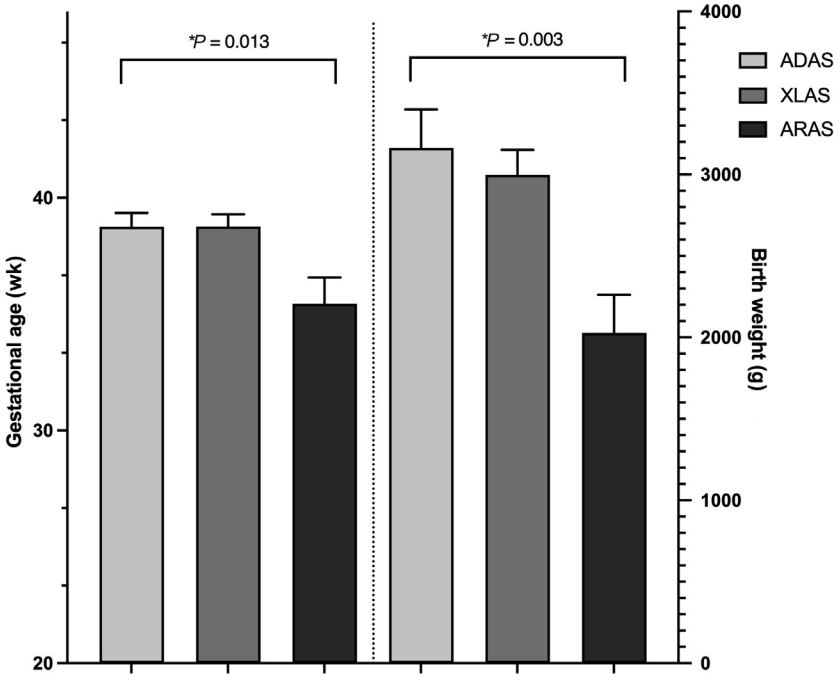


Figure 1 | Marginal mean duration of pregnancy and birth weight, stratified per inheritance pattern. Marginal means are adjusted for covariates pre-pregnancy serum creatinine concentration, pre-pregnancy proteinuria, and chronic hypertension in multilevel analysis (generalized estimating equations). Autosomal recessive Alport syndrome (ARAS)–inheritance pattern was an independent predictor for lower birth weight ($P = 0.003$) and shorter duration of pregnancy ($P = 0.013$). In autosomal dominant Alport syndrome (ADAS), X-linked Alport syndrome (XLAS), and ARAS pregnancies, adjusted marginal mean birth weight was 3162 g (SEM, 238 g; n = 26), 2997 g (SEM, 154 g; n = 68), and 2027 g (SEM, 235 g; n = 7; $P = 0.003$), respectively. Adjusted marginal mean duration of pregnancy was 38.75 weeks (SEM, 0.60 weeks; n = 26), 38.76 weeks (SEM, 0.53 weeks; n = 71), and 35.44 weeks (SEM, 1.13 weeks; n = 7; $P = 0.013$), respectively.

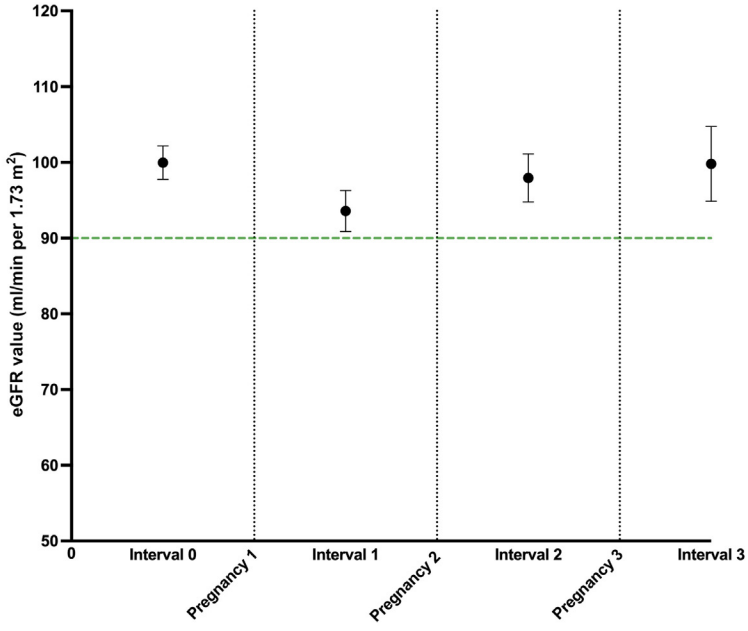
pregnancy interval 2, mean eGFR decline was –2.04 ml/min per 1.73 m^2 (SEM, 3.53 ml/min per 1.73 m^2; 95% confidence interval, –8.96 to 4.89 ml/min per 1.73 m^2) over 3.83 years (IQR, 7.67 years). After third pregnancy, mean eGFR decline was –0.18 ml/min per 1.73 m^2 (SEM, 5.55 ml/min per 1.73 m^2; 95% confidence interval, –11.05 to 10.70 ml/min per 1.73 m^2) over 7.33 years (IQR, 9.75 years). Figure 2 illustrates adjusted marginal means of eGFR per pregnancy interval. Despite a stepwise decline in eGFR after first pregnancy, pregnancy had no significant accelerating effect on eGFR decline ($P = 0.144$). The interaction term was not significant for pregnancy interval 1 (β, –0.64; SEM, 0.35; $P = 0.069$), pregnancy interval 2 (β, –0.061; SEM, 0.44; $P = 0.890$), and pregnancy interval 3 (β, –0.51; SEM, 0.70; $P = 0.467$). Therefore, pregnancy did not have an additional effect on eGFR slope (overall pre-pregnancy β = –1.030; postpregnancy [includes intervals 1, 2, and 3] β = –1.349; $P = 0.386$). Figure 3 shows the adjusted estimated marginal means of eGFR visualized in years of follow-up before and after first pregnancy.

Other predictors that affect eGFR

To determine the effect and to adjust for it, other possible predictors for eGFR were analyzed (Table 4). For this analysis, the variable "after first pregnancy" designated all eGFR measurements before and after first pregnancy. The variables after first pregnancy, pre-pregnancy SCr, proteinuria pre-pregnancy, chronic hypertension, and XLAS and ARAS inheritance patterns were significantly associated with lower eGFR values in multilevel analysis adjusted for age at eGFR measurement. These variables were added to the multivariable model, including the interaction term "after first pregnancy × age at eGFR measurement," to see if eGFR slope differed per pregnancy interval when adjusted for these factors. eGFR slope after first pregnancy was not different, adjusted for the above mentioned factors ($P = 0.566$).

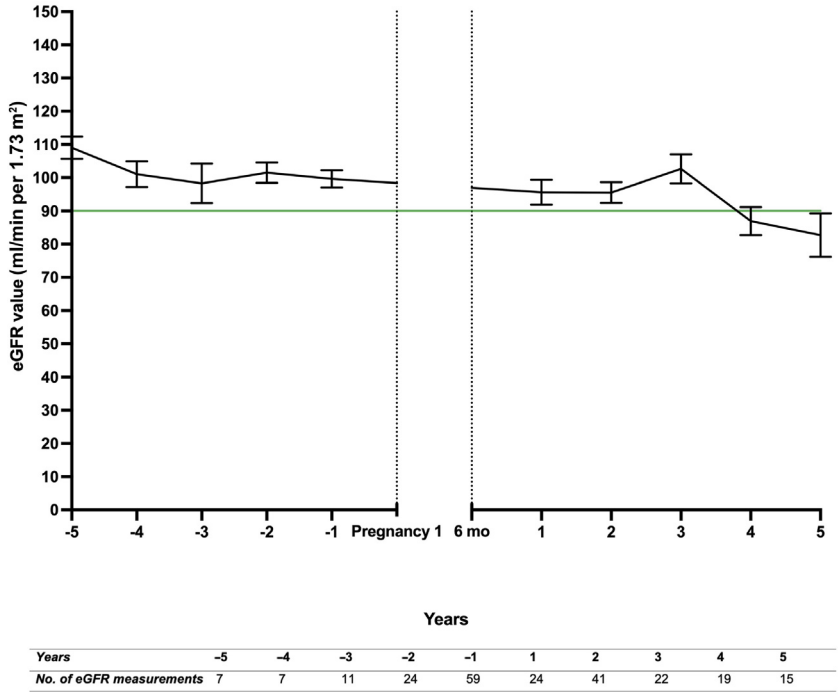
DISCUSSION

Our study has 4 key findings. First, this is the largest cohort of pregnancies in women with *COL4A3-5*–related disease to date. We show that overall neonatal pregnancy outcomes



	Interval 0	Interval 1	Interval 2	Interval 3
No. of eGFR measurements	124	121	85	31
Women included	76	73	41	13
Follow-up time in years per pregnancy interval (IQR)	1.10 (1.84)	1.92 (2.70)	3.83 (7.67)	7.33 (9.75)
eGFR decline per pregnancy interval	Ref	−6.40 ml/min per 1.73 m^2 (2.25), $P = 0.004$	−2.04 ml/min per 1.73 m^2 (3.53), $P = 0.564$	−0.18 ml/min per 1.73 m^2 (5.55), $P = 0.975$

Figure 2 | Adjusted marginal means of estimated glomerular filtration rate (eGFR) before and after pregnancies, stratified per pregnancy interval (n = 110 patients). The green line represents the eGFR of 90 ml/min per 1.73 m^2. eGFR decline per pregnancy interval is shown in marginal means (SEM). Annual eGFR decline in the cohort was –1.47 ml/min per 1.73 m^2 (SEM, 0.15 ml/min per 1.73 m^2). In this model, "age at eGFR measurement" was used as a continuous covariate, and "pregnancy interval" was used as a categorical factor. Error bars represent SEM. IQR, interquartile range; Ref, reference.



Years	-5	-4	-3	-2	-1	1	2	3	4	5
No. of eGFR measurements	7	7	11	24	59	24	41	22	19	15

Figure 3 | Adjusted marginal means of estimated glomerular filtration rate (eGFR) before and after pregnancy first pregnancy. The green line represents the eGFR of 90 ml/min per 1.73 m^2. In this model, "age at eGFR measurement" was used as a continuous covariate, and "years before or after pregnancy" was used as a categorical factor. Error bars represent SEM.

in mild AS are excellent with live births reported after 20 weeks' gestation, median gestational age, and mean birth weight comparable to general population data. Second, despite an eGFR step decline after first pregnancy, overall mean eGFR after pregnancy remains >90 ml/min per 1.73 m^2. Furthermore, pregnancy does not affect eGFR slope after pregnancy. Together, these reassuring results point out that women with mild stage AS should not be dissuaded from becoming pregnant. Third, ARAS-inheritance pattern shows less favorable pregnancy outcomes. Finally, ARAS-inheritance pattern is an independent predictor for lower birth weight and duration of pregnancy when adjusted for classic risk factors, such as pre-pregnancy kidney function, pre-pregnancy proteinuria, and chronic hypertension, that also show (borderline) significance. The small number of ARAS pregnancies (n = 12) should be considered when interpreting this analysis. Furthermore, in this study, *COL4A3/COL4A4* heterozygotes were considered as having ADAS. The significant different outcomes of ARAS pregnancies should be interpreted in the context of comparing them with XLAS pregnancies (66% of cohort) and the relatively mild ADAS pregnancies (24% of cohort).

Table 4 | Effect of predictors on eGFR slope (multilevel analysis)

Variables	β coefficient	SEM	*P* value
After first pregnancy	**−5.59**	**2.17**	**0.010**
Age at pregnancy	0.21	0.42	0.617
BMI before pregnancy	0.55	0.40	0.161
Nullipara	−3.78	2.78	0.174
Serum creatinine pre-pregnancy, μmol/L	**−0.76**	**0.10**	**<0.001**
Chronic hypertension	**−10.63**	**5.34**	**0.047**
Proteinuria pre-pregnancy	**−13.81**	**3.55**	**<0.001**
Inheritance pattern			
ADAS	0 (Reference)	–	–
XLAS	**−10.14**	**3.59**	**0.005**
ARAS	**−33.42**	**8.10**	**<0.001**
Glycine substitution	10.60	16.27	0.515
Variant type	NA	NA	0.407
Decennium of pregnancy	NA	NA	0.099

–, not applicable because of reference; ADAS, autosomal dominant Alport syndrome; ARAS, autosomal recessive Alport syndrome; BMI, body mass index; eGFR, estimated glomerular filtration rate; XLAS, X-linked Alport syndrome.
In multilevel analysis, age at eGFR measurement (years) was used as a continuous covariate. All variables were tested in multilevel analysis, adjusted for the effect of time. The dichotomous variable "after first pregnancy" appoints timing of eGFR measurement before/after first pregnancy, with after first pregnancy including the time period of pregnancy interval 1 to 3. Bold parameters are significant ($P < 0.05$).

In this cohort reflecting daily clinical practice of Alport pregnancies, proper quantifiable proteinuria values were missing in 70% of pregnancies, which hinders adjustment in analyses. A bias toward testing after first detection of proteinuria further hinders interpretation of this parameter.

Next to classic risk factors (pre-pregnancy eGFR, proteinuria, and chronic hypertension), different inheritance patterns could be considered when counseling. This study shows the relevance of investigating pregnancy outcomes stratified per cause of kidney disease and the benefits of tailored pre-pregnancy counseling and care for women with CKD.

Furthermore, although the eGFR step decline after first pregnancy was significant, eGFR after second and third pregnancy was not significantly lower. The significant decline

Table 5 | Comparison to other cohorts for CKD and pregnancy (Piccoli *et al.*, 2015,[4] Bramham/Wiles 2017–2021[44] [not all pregnancies in this cohort have been previously published], and Dutch General Population 2018[45])

Variable	ALPART cohort CKD G1 (N = 102)	ALPART cohort CKD G2 (N = 23)	Bramham/Wiles CKD G1 (N = 99)	Bramham/Wiles CKD G2 (N = 45)	TOCOS cohort[a] CKD G1 (N = 370)	TOCOS cohort[a] CKD G2 (N = 87)	Dutch general population 2018
Baseline characteristics							
Maternal age, median (IQR), yr	29.3 (6.9)	31.1 (4.4)	33.6 (5.3)	33.8 (5.7)	31.3 (5.5)	33.8 (4.5)	20 – >40
Parity, nulliparous	56/96 (58)	13/21 (62)	36/99 (36)	12/45 (27)	55	58	44
Chronic hypertension	12/101 (12)	4/19 (21)	38/99 (38)	26/45 (58)	80/370 (22)	36/87 (41)	NR
Proteinuria	58/87 (67)	18/18 (100)	61/99 (62)	14/24 (58)	0.12 (0–14.6)[b]	0.15 (0–6.8)[b]	NR
Pregnancy outcomes							
Gestational age at delivery, median (IQR) and mean (SD), wk	**39.0 (2.39) 38.3 (2.52)**	**38.0 (3.14) 37.6 (2.71)**	**38.1 (36.1–40.1) 37.23 (2.98)**	**37.6 (34.9–40.3) 36.81 (2.46)**	**37.6 (2.6)**	**35.7 (3.2)**	**39.5**
Preterm delivery							
<37 wk	18/100 (18)	7/23 (30)	24/99 (24)	16/45 (36)	24	51	7
<34 wk	6/100 (6)	4/23 (17)	14/99 (14)	7/45 (16)	7	21	2
Birth weight, median (IQR), g	**3158 (728)**	**2669 (688)**	**2787 (713)**	**2625 (627)**	**2967 (659)**	**2484 (707)**	**3364**
Gestational hypertension	20/91 (22)	6/18 (33)	2/56 (3.6)	1/5 (20)	23/290 (8)	9/51 (18)	5.3
New-onset/doubling proteinuria	35/48 (73)	7/9 (78)	42/75 (56)	0/14	76/370 (21)	33/87 (38)	NR

ALPART, mAternal and foetal PregnAncy outcomes of women with AlpoRt syndrome; CKD, chronic kidney disease; IQR, interquartile range; NR, not reported; TOCOS, Torino-Cagliari Observational Study.

[a]TOCOS cohort included 62% and 43% estimated glomerular filtration rate measurements at first checkup during pregnancy. The classification of CKD categories during pregnancy possibly underestimates CKD category because of glomerular hyperfiltration in the beginning of pregnancy.

[b]Measurement in g/d.

Differences between cohorts on baseline level are: (i) ALPART cohort lower maternal age compared with other cohorts; (ii) ALPART cohort higher incidence nulliparous women; (iii) ALPART cohort lower incidence of chronic hypertension; and (iv) ALPART cohort higher incidence of pre-pregnancy proteinuria compared with UK cohort (TOCOS cohort not comparable). The most important differences in fetal outcome are shown in bold. Differences between cohorts in outcomes are mainly shown in CKD G1 pregnancies: (i) ALPART cohort higher mean gestational age at delivery; (ii) ALPART cohort lower incidence preterm birth; (iii) ALPART cohort higher mean birth weight; and (iv) ALPART cohort higher incidence gestational hypertension during pregnancy. Data are presented as mean (SD) and number/total (percentage) unless stated otherwise. Not all pregnancy outcomes were available for all pregnancies. For categorical variables, incidences are shown as numerator/denominator.

after first pregnancy might be attributed to almost half of the cohort having only 1 pregnancy. For reasons that could not be retrieved in retrospect (but might be the occurrence of complications during pregnancy or decrease of kidney function), these women have not conceived again. Therefore, the nonsignificant effect of pregnancy on eGFR slope might be overestimated because of "more healthy women" having multiple pregnancies. The lacking validity of the Chronic Kidney Disease Epidemiology Collaboration formula for eGFR values >90 ml/min challenges interpretation of the step decline. Still, because of mean eGFR values remaining >90 ml/min per 1.73 m^2, clinical significance of this effect is questionable.

Our cohort mainly consisted of women with early CKD (G1–G2) or women with only hematuria without eGFR decline pre-pregnancy, which seems to be the disease category of most *COL4A3-5* women during reproductive age.[19–21,23,25,26,46,47] Our finding of favorable pregnancy outcomes and long-term kidney outcomes aligns with previous studies.[26] These studies also reported remarkable increases of proteinuria during pregnancy. This matches our finding of 76% new onset or doubling of proteinuria, although this parameter is likely skewed because of 60% to 70% missing quantifiable proteinuria measurements. The finding of most proteinuria values restoring to baseline postpartum was likewise skewed.

Baseline characteristics and pregnancy outcomes of CKD G1 to G2 pregnancies in the ALPART cohort, the UK cohort,[44] the Italian Torino-Cagliari Observational Study (TOCOS) cohort,[4] and the Dutch general populations are compared in Table 5. At baseline, the ALPART cohort shows lower maternal age, higher nulliparity, and higher pre-pregnancy proteinuria rates and lower chronic hypertension rates. Overall, neonatal outcomes are most favorable in the G1-ALPART cohort. The longer duration of pregnancy and higher mean birth weight are positive factors for infant neurodevelopment.[48–51] A possible explanation for these differences might be the underestimation of CKD categories in the TOCOS cohort, by partly determining CKD categories during pregnancy, and overestimating kidney function attributable to physiological gestational hyperfiltration.[3,4,7] Furthermore, modifying effects of cause of kidney disease could also explain different outcomes. This specific effect should be further analyzed in future research, correcting not only for CKD category, but also for presence of chronic hypertension and pre-pregnancy proteinuria.

Maternal outcomes, such as new-onset or doubling of proteinuria and gestational hypertension, show higher incidences in the ALPART cohort. Although proteinuria values are likely skewed, as mentioned above, this difference could be partly explained by the pathophysiology of *COL4A3-5*–related disease with leaking glomerular basement membrane

and an increased renal blood flow during pregnancy.[3,6] The higher incidence of gestational hypertension might be attributable to lower incidence of chronic hypertension. Nevertheless, the higher incidence of gestational hypertensive complications during pregnancy, also compared with the Dutch general population, implies suboptimal adaptation to pregnancy in women with *COL4A3-5*–related disease.

Furlano *et al.* recently reported on clinical features of patients with ADAS, of whom 56% were female.[15] They showed an eGFR decline of –1.46 ml/min per 1.73 m^2 per year. Nothing was reported on pregnancy. Our overall eGFR decline of –1.47 ml/min per 1.73 m^2, and no significant difference in eGFR slope after pregnancy, matches this finding. Unfortunately, there is no validated formula for eGFR values >90 ml/min. Therefore, translation of absolute decline in eGFR after pregnancy to years of eGFR loss cannot be reliably made.

This is the largest cohort of pregnancies in women with *COL4A3-5*–related disease. Thanks to an international collaboration with 17 medical centers, we have been able to collect a large cohort and to provide valuable information for the clinician in counseling women with *COL4A3-5*–related disease who want to conceive. Furthermore, rigorous quality control of the data was undertaken, and much effort was undertaken to obtain information on missing values. In the ALPART cohort, women with a confirmed genetic diagnosis and/or clinical diagnosis were included. Despite >80% of women showing clinical signs of AS pre-pregnancy, some women who received a genetic diagnosis after pregnancy may not have exhibited clinical features of CKD before pregnancy already.[35] This information could not be obtained retrospectively. It can be hypothesized that these women with less severe disease have biased results in overestimating our positive results (see Supplementary Tables S5 and S6 for baseline characteristics and pregnancy outcomes stratified on diagnosis before pregnancy). Furthermore, this study can only describe the selection of women with *COL4A3-5*–related disease within families who presented in the hospital and got tested. Nevertheless, this does not have to be problematic, because study results are applicable to this selection that seeks pre-pregnancy counseling. Furthermore, this cohort is built up via a European Rare Kidney Disease Reference Network survey, and coverage is limited to the knowledge and geographic locations of participants and our international network. Also, inclusion of pregnancies from different countries within a large time span hindered interpretation of outcomes that are influenced by era- and country-dependent clinical management, such as induction of delivery, shortening duration of pregnancy. Nevertheless, a comparison between deliveries before and after 2010 (Supplementary Tables S7 and S8) showed overall similar outcomes. Furthermore, in this international collaboration, differences in international privacy legislation had to be considered. To lower the threshold of participating in our study, only general information on *COL4A3-5* genotype was gathered. Therefore, information on base pair alterations was not available, and detailed analyses on genotype-phenotype correlations were hindered. Another limitation of this study is the retrospective study design and the forthcoming missing values and bias. Pre-pregnancy CKD category was missing in 33% of pregnancies. It is especially unfortunate that there was a lack of uniform measurements of proteinuria, a primary feature of AS that could not be properly analyzed in this study.

Our results are highly relevant to clinicians, enabling them to provide personalized pre-pregnancy counseling to patients with *COL4A3-5*–related disease, including stratification on inheritance patterns. Given the reassuring maternal and neonatal results in mild disease stages of AS, there is no reason to dissuade these women from becoming pregnant. Furthermore, it is recommended to optimize disease control before pregnancy in women with CKD. Ideally, patients with AS should be offered pre-pregnancy counseling, opportunity to optimize proteinuria and blood pressure control, consideration of aspirin, and risk stratification for pregnancy care. This also includes being alert to other individuals at risk for AS in their families.

Future research should focus on comparing kidney disease–specific pregnancy outcomes with CKD in general. It is a challenge to find comparable cohorts. Therefore, we have established the PREGeNEPH registry (Pregnancy, Genetics and Nephrology), in which we investigate the influence of specific causes of CKD, next to known risk factors for pregnancy outcomes, such as pre-pregnancy kidney function, chronic hypertension, and proteinuria. In the future, this registry will also gather data prospectively to diminish missing values issues, which are prevalent in current retrospective CKD and pregnancy research.

We conclude that overall neonatal pregnancy outcomes in women with mild *COL4A3-5*–related disease are favorable. Mean eGFR declines significantly after pregnancy but remains >90 ml/min per 1.73 m^2. Overall, pregnancy does not significantly affect eGFR slope. ARAS is associated with a higher incidence of preterm birth and is an independent risk factor for lower birth weight, although conclusions should be nuanced because of a small number of ARAS pregnancies and adjustment for pre-pregnancy proteinuria being hindered by missing values. Next to classic risk factors, inheritance pattern could be considered in counseling. With 192 pregnancies from 17 different international centers, this is the largest study to date in this relatively rare disease. This study shows the relevance of investigating pregnancy outcomes in specific kidney disease causes rather than CKD in general.

DISCLOSURE

All the authors declared no competing interests.

DATA STATEMENT

The data supporting the findings of this study are available on submission of a request that will be reviewed by the ALPART working group. Onsite access to the data for verification purposes can be arranged.

FUNDING

This work was supported by the "Stichting Vrienden van het UMC Utrecht," on behalf of the "Elisabeth von Freyburg Stichting" and the "Van Dam-Van Os Stichting" (grant 15121404).

ACKNOWLEDGMENTS

Eleven of the authors of this publication are members of the European Reference Network for Rare Kidney Diseases (ERKNet). We thank the entire ALPART study network for their contribution to this study and the continued collaboration on pregnancy in (rare) kidney disease. Furthermore, we thank the members of the ERKNet Working Group "Hereditary Glomerulopathies" for their contributions and support.

Published abstracts

- Gosselink ME, Snoek R, Van Bakel S, et al. International pregnancy outcomes in Alport syndrome (*COL4A3-5* related disease) vs. CKD in general. *J Am Soc Nephrol.* 2022;33:264.
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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Methods. Additional definitions of study parameters.
Supplementary Figure S1. Flowchart of this study.
Supplementary Table S1. Overview of included pregnancies from each participating center.
Supplementary Table S2. Description of complex suspected digenic phenotypes.
Supplementary Table S3. Baseline characteristics of preterm births.
Supplementary Table S4. Baseline characteristics stratified per inheritance pattern.
Supplementary Table S5. Baseline characteristics stratified on established diagnosis: before pregnancy and after pregnancy.
Supplementary Table S6. Pregnancy outcomes stratified on established diagnosis: before pregnancy and after pregnancy.
Supplementary Table S7. Baseline characteristics stratified on era: delivery before and after 2010.
Supplementary Table S8. Pregnancy outcomes stratified on era: delivery before and after 2010.

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