The Effects of Pregnancy on Disease Progression of Retinitis Pigmentosa

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• PURPOSE: Retinitis pigmentosa (RP) is the most common diagnosis in the ophthalmic genetics clinic. Women with RP are often diagnosed during their reproductive years, posing significant challenges for family planning. The effects of pregnancy on RP progression is a frequently unanswered concern for these patients.
• DESIGN: Retrospective cohort study.
• SUBJECTS: Women who attended Moorfields Eye Hospital (London, UK) and met the following inclusion criteria were included in this study: (1) had their most recent visit at 30 years old or more, (2) were diagnosed with RP, (3) had information in their medical records about having had children, and (4) were found to have biallelic rare or likely disease-causing variants in *USH2A*.
• METHODS: The cohort was divided into parous and nulliparous, and multivariate Cox regressions adjusting for multiple confounding effects were performed. A further analysis also included number of children as a variable.
• MAIN OUTCOME MEASURES: RP severity criteria based on visual acuity (VA) and ellipsoid zone (EZ) width, and national registration of sight impairment.
• RESULTS: A total of 142 women were included in the study, 98 parous (69%) and 44 nulliparous (31%). In the parous group, 21% had cystoid macular edema (CMO) requiring treatment and 46% had cataracts or were pseudophakic, versus 18% with CMO and 59% with cataracts in the nulliparous. Women had a median of 2 children. A significant association was only found in parous women having 3.04 (1.23-7.48) times increased risk of having VA worse than LogMAR 0.7 than nulliparous ($P = .016$), after adjusting for baseline age, phenotype, lens status, and CMO.
• CONCLUSIONS: This is the first large-scale objective study analyzing the effects of pregnancy in genetically-confirmed women with RP. Women with *USH2A*-associated RP who had children appeared to have 3.04 times the risk of reaching VA below 20/100 than those who did not have children. It is possible that other factors besides retinal degeneration are affecting central vision and causing this increased risk. A significant association between faster or slower EZ loss and pregnancy was not present in our cohort. We believe these findings will be relevant to all women with RP considering starting a family; although further studies are needed. (Am J Ophthalmol 2025;271: 243–249. © 2024 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/))

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INTRODUCTION

Pregnancy induces significant physiological changes that affect the function and metabolism of all body systems, which are crucial for fetal development.[1] Some of the most important changes include increased plasma volume and cardiac output,[2] glomerular hyperfiltration (impacting drug clearance and electrolyte balance),[3] increased tidal volume and reduced residual lung capacity,[4] and major endocrine changes led by estrogen, progesterone, human chorionic gonadotropin hormone, and human placental lactogen, which alter insulin sensitivity and thyroid function.[5]

Ocular changes and complications that may occur during pregnancy include corneal thickening,[6] decreased intraocular pressure,[7] gestational hypertension-related retinopathy and optic neuropathy, serous retinal detachment, and central serous chorioretinopathy.[8] Parity has also been associated with an increased risk of developing cataracts.[9,10] Pregnancy and lactation can influence the management of preexisting ocular conditions, such as glaucoma, diabetic retinopathy, and inherited retinal disorders (IRD) like retinitis pigmentosa (RP); in terms of suitable medication (glaucoma and RP-associated cystoid macular edema [CMO]), and accelerated disease progression in diabetic retinopathy.

RP is the most common diagnosis in the ophthalmic genetics' clinic, classically characterized by peripheral field constriction, night blindness, and maintained central vision until late disease stages. Women with RP are often diagnosed during working and fertile age, posing significant challenges while making life-changing decisions such as choosing a career and planning a family.[11] Furthermore, patients with IRD often experience CMO, which may de-

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crease their visual acuity (VA) or contrast sensitivity.[12] This is often managed with topical or oral medication such as dorzolamide, brinzolamide and acetazolamide; all of these being category C drugs, meaning that they can be given to pregnant women if the benefit to the mother outweighs the risk to the fetus.

Normal pregnancy is considered to be a mild state of oxidative stress,[13] with this balance exacerbated during complications. The unique hyperestrogenism that occurs during pregnancy may present challenges for preexisting conditions including those of genetic etiology. In this study, we aim to explore a common question in clinical practice: is RP going to get worse/increase its rate of progression during/after pregnancy? Possible associations are analyzed in detail, considering multiple confounding characteristics, and ultimately shedding light on this important topic.

PATIENTS AND METHODS

• **STUDY DESIGN AND PARTICIPANTS:** Women who attended Moorfields Eye Hospital (MEH, London, UK) and met all the following inclusion criteria were included: (1) had their most recent visit at 30 years old or more, (2) were diagnosed with an IRD, (3) had information in their medical records about having children, and (4) were found to have biallelic rare or likely disease-causing variants in *USH2A* through panel-based targeted next generation sequencing, exome sequencing, or genome sequencing. Patients were identified through the inherited eye disease database at MEH, including patients who attended MEH between 1950 and 2024. Informed consent was obtained from all patients. Ethical approval was provided by the local ethics committee and the study honored the tenets of the Declaration of Helsinki.

USH2A was chosen due to being the most common gene to cause both isolated RP and Usher syndrome (USH; RP with hearing impairment) at MEH, and to limit the confounding effect of different genotypes.[14] Considering that individuals with USH often have a more severe retinal phenotype than those with isolated IRD, the results were adjusted to avoid a confounding effect.[15] Patients who had children after their latest visit at MEH ($n = 2$) were considered as without children for study purposes.

• **OUTCOMES:** Relevant patient data was retrieved from the electronic healthcare record and imaging software systems. For each of the metrics described below, we considered the time since first seen in the hospital until the event occurred or the patient was last seen.

Snellen best-corrected VA (BCVA) was recorded and converted to LogMAR for statistical purposes. Count fingers vision corresponds to LogMAR 1.98, hand motion to LogMAR 2.28, light perception to LogMAR 2.7, and no light perception to LogMAR 3.0.[16,17]

Quantitative measurements on spectral-domain optical coherence tomography (OCT, Heidelberg Spectralis, Heidelberg Engineering, Inc.) consisted of measuring the ellipsoid zone (EZ) width at the foveal scan.

The RP severity criteria were based on Iftikhar et al., using the following BCVA ranges: 20/32 or worse (LogMAR 0.2 or higher), 20/40 or worse (LogMAR 0.3 or higher), equal to 20/100 or worse (LogMAR 0.7 or higher), and worse than 20/100 (LogMAR greater than 0.7). For EZ scores, the thresholds were if the EZ line occupied ≥15° of the foveal line scan, ≥10°, ≥7°, or ≥5°.[18] We also considered if EZ >600 μm (~2°), which is a threshold that has been associated with better visual prognosis after cataract surgery in patients with RP.[19] Furthermore, age at registration in the national visual impairment registry was also taken into account. In the United Kingdom, patients are generally registered sight impaired (SI, partially sighted) if a large part of their visual field is missing or if their BCVA is ≤ 6/24 with a moderate reduction of visual field. To be registered as severely sight impaired (SSI, blind), the visual field needs to be significantly reduced or BCVA needs to be <6/60 with a reduction of visual field (https://www.gov.uk/government/publications/guidance-published-on-registering-a-vision-impairment-as-a-disability). Patients who were directly registered as SSI, without previously being SI, were not taken into consideration for SI statistical analysis but were included for SSI only.

• **DATA ANALYSIS:** For all metrics described above, the association between parity status (parous and nulliparous) and the above metrics was assessed using a univariable and multivariable Cox regression, adjusted for (1) age at baseline, (2) isolated RP versus USH, (3) visually significant cataract/pseudophakia, and (4) presence of CMO that required treatment. Time-to-event outcomes were reported using standard survival analysis based on the Kaplan–Meier method.

A further analysis was undertaken solely on the group of parous women, where number of children was modeled continuously and categorically (≤2 vs >2) and the association between number of children and the metrics was assessed using a multivariable Cox regression, adjusted for (1) age at baseline, (2) isolated RP versus USH, (3) cataract/pseudophakia, and (4) presence of CMO that required treatment.

Statistical analysis was undertaken with GraphPad Prism 9.4.1 (GraphPad Software) and STATA 18.0 (StataCorp). The threshold of significance was set at $P < .05$.

RESULTS

One hundred and sixty-eight women with *USH2A*-associated IRD were screened for eligibility. One hundred and forty-two women (84.5%) met all inclusion criteria

TABLE 1. Baseline Characteristics, Outcomes, and Descriptive Statistics in the Parous and Nulliparous Groups

Baseline Characteristics and Outcomes	Parous ($n = 98$)	Nulliparous ($n = 44$)
Age at baseline (y)		
Median (range)	41 (12-79)	35 (20-74)
CMO requiring treatment during fertile years?		
No	77 (79%)	36 (82%)
Yes	21 (21%)	8 (18%)
Cataract		
No	53 (54%)	18 (41%)
Yes	45 (46%)	26 (59%)
Isolated RP/Usher syndrome		
RP	52 (53%)	22 (50%)
USH	46 (47%)	22 (50%)
Number of children		
≤2	71 (72%)	N/A
>2	27 (28%)	N/A
Median (range)	2 (1-6)	N/A
SI	25 (34.2%)	18 (54.6%)
Median time to event (95% CI)	NR	11 (3-NR)
Event-free at 5 y FU (95% CI)	70 (57%-80%)	63 (44%-77%)
Event-free at 10 y FU (95% CI)	60 (45%-72%)	52 (33%-68%)
SSI	43 (44%)	19 (43%)
Median time to event (95% CI)	12 (7-20)	17 (10-NR)
Event-free at 5 y FU (95% CI)	74 (63%-82%)	78 (63%-88%)
Event-free at 10 y FU (95% CI)	56 (44%-67%)	64 (47%-77%)
EZ <600 µm	33 (36%)	11 (25%)
Median time to event (95% CI)	17 (14-27)	21 (20-NR)
Event-free at 5 y FU (95% CI)	85 (76%-91%)	93 (80%-98%)
Event-free at 10 y FU (95% CI)	73 (61%-82%)	85 (69%-93%)
EZ ≤5°	41 (55%)	23 (52%)
Median time to event (95% CI)	12 (9-15)	15 (10-NR)
Event-free at 5 y FU (95% CI)	74 (63%-82%)	79 (64%-89%)
Event-free at 10 y FU (95% CI)	55 (43%-66%)	67 (50%-79%)
EZ ≤7°	62 (67%)	34 (77%)
Median time to event (95% CI)	9 (6-12)	8 (5-10)
Event-free at 5 y FU (95% CI)	61 (50%-71%)	66 (50%-78%)
Event-free at 10 y FU (95% CI)	45 (33%-56%)	35 (21%-50%)
EZ ≤10°	76 (83%)	41 (93%)
Median time to event (95% CI)	7 (3-9)	7 (5-8)
Event-free at 5 y FU (95% CI)	55 (44%-65%)	58 (42%-71%)
Event-free at 10 y FU (95% CI)	32 (22%-43%)	21 (10%-34%)
EZ ≤15°	87 (95%)	44 (100%)
Median time to event (95% CI)	2 (0.1-5)	5 (2-7)
Event-free at 5 y FU (95% CI)	39 (28%-48%)	44 (29%-58%)
Event-free at 10 y FU (95% CI)	22 (14%-31%)	12 (4%-24%)
BCVA ≤20/32	78 (80%)	39 (89%)
Median time to event (95% CI)	0.1 (0.01-0.1)	0.1 (0.01-3)
Event-free at 5 y FU (95% CI)	23 (15%-32%)	32 (19%-45%)
Event-free at 10 y FU (95% CI)	18 (11%-27%)	9 (2%-21%)
BCVA ≤20/40	61 (62%)	30 (68%)
Median time to event (95% CI)	6 (2-10)	11 (3-14)
Event-free at 5 y FU (95% CI)	51 (41%-61%)	63 (48%-76%)
Event-free at 10 y FU (95% CI)	36 (25%-47%)	53 (37%-67%)
BCVA ≤20/100	47 (48%)	18 (41%)
Median time to event (95% CI)	9 (8-20)	16 (12-NR)
Event-free at 5 y FU (95% CI)	71 (61%-79%)	82 (67%-90%)
Event-free at 10 y FU (95% CI)	44 (32%-55%)	70 (53%-82%)
BCVA <20/100	31 (32%)	6 (14%)
Median time to event (95% CI)	20 (16-32)	22 (22-NR)
Event-free at 5 y FU (95% CI)	84 (74%-90%)	93 (80%-98%)
Event-free at 10 y FU (95% CI)	78 (67%-85%)	88 (73%-95%)

Median time to event represents the median time in which 50% of individuals have had the event.

BCVA = best-corrected visual acuity; CI = confidence interval; CMO = cystoid macular edema; EZ = ellipsoid zone; FU = follow-up; NR = not reached; RP = retinitis pigmentosa; SI = sight impaired; SSI = severely sight impaired; USH = usher syndrome; y = years.

and were included in the study. Ninety-eight women were parous (69%) and forty-four nulliparous (31%, Table 1). One hundred and thirty-six (96%) had OCT scans and EZ width available.

The parous group was composed of 52 patients (53%) with isolated RP and 46 with USH (47%). The age at their baseline visit was 41.7 ± 13.6 years old (median 41, range 12-79), and the age at the most recent visit was 54 ± 13.2 years old (median 54.5, range 28-88), with a mean follow-up time of 12.3 ± 9.3 years (median 10, range 0-43). Twenty-one women (21%) had CMO which required topical or oral treatment during fertile years. Forty-five (46%) had visually significant lens opacities or were pseudophakic. Women had a median of 2 children (range 1-6), with 27 (28%) having more than 2 children and 71 (72%) having only 1 or 2.

The nulliparous group had 22 patients with isolated RP (54%) and 22 with USH (46%). The age at baseline visit was 38.4 ± 14 years old (median 35, range 20-74), and the age at the most recent visit was 52.7 ± 13.9 years old (median 51, range 30-80), with a mean follow-up time of 14.2 ± 7 years (median 15, range 0 to 34). Eight (18%) had CMO during fertile years, requiring topical or oral treatment. Twenty-six (59%) had visually significant lens opacities or were pseudophakic.

There was not a significant difference between age at baseline in both groups (*t* test $P = .0895$). Forty-three patients (30%) were registered as SI, 62 (44%) as SSI, 64 (45%) had an EZ width ≤5°, and 37 (26%) had BCVA worse than LogMAR 0.7 (Table 1).

The results of the Cox regression showed that parous women had 2.74 (95% CI:1.13-6.65) times the risk of having BCVA worse than LogMAR 0.7 compared to nulliparous ($P = .026$, Figure 1A). After adjusting for age at baseline, RP versus USH phenotype, cataract, and CMO, the risk remained statistically significant, with 3.04 (1.23-7.48) times increased risk of having BCVA worse than LogMAR 0.7 ($P = .016$, Figure 1B). There was also a near-significant association with BCVA worse or equal to LogMAR 0.7, with parous women having 1.64 (0.94-2.85)

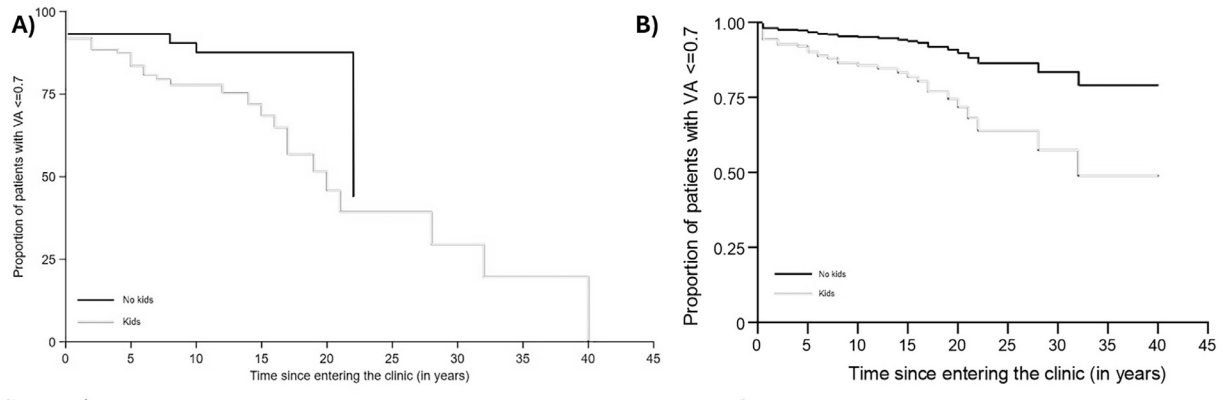

FIGURE 1. Graphic representation of time to VA <0.7 LogMAR, divided in parous and nulliparous, since first seen in the hospital. (A) Analysis unadjusted for other variables. Parous women had 2.74 (95% CI:1.13-6.65) times the risk of having BCVA worse than LogMAR 0.7 than nulliparous ($P = .026$). Median time to event was 20 (95% CI 16-32) years old for the parous group, versus 22 (95% CI 22-NR) years old for nulliparous women. (B) Analysis adjusted for all confounding variables, including cataract, CMO, age at baseline, and phenotype. Parous women had 3.04 (1.23-7.48) times the risk of reaching this level of VA than nulliparous ($P = .016$).

TABLE 2. Univariate and Multivariate Cox Models Analyzing Differences Between Parous and Nulliparous Groups.

Metrics	Univariate Cox Model		Multivariate Cox Model	
	HR (95% CI) Kids Vs No kids	*P* Value	HR (95% CI) Kids Vs No kids	*P* Value
Registration status				
Sight impaired	0.71 (0.39-1.31)	.28	0.8 (0.42-1.52)	.5
Severely sight impaired	1.24 (0.72-2.14)	.44	1.18 (0.68-2.06)	.55
Ellipsoid zone (EZ) width				
EZ <600 μm	1.72 (0.85-3.46)	.13	1.58 (0.77-3.23)	.21
EZ ≤15°	0.91 (0.62-1.33)	.63	0.75 (0.51-1.12)	.16
EZ ≤10°	0.83 (0.56-1.22)	.34	0.72 (0.48-1.07)	.11
EZ ≤7°	0.9 (0.59-1.38)	.65	0.83 (0.53-1.29)	.41
EZ ≤5°	1.22 (0.74-2.02)	.44	1.12 (0.67-1.87)	.67
Best-corrected visual acuity (LogMAR)				
BCVA ≥ 0.2	1.01 (0.69-1.49)	.94	1 (0.68-1.49)	.99
BCVA ≥ 0.3	1.26 (0.81-1.97)	.31	1.19 (0.76-1.88)	.44
BCVA ≥ 0.7	**1.64 (0.94-2.85)**	**.079**	**1.72 (0.98-3.01)**	**.058**
BCVA >0.7	**2.74 (1.13-6.65)**	**.026**	**3.04 (1.23-7.48)**	**.016**

Bold values indicate significant ($p < 0.05$) and near significant associations.

times the risk of getting to this acuity level than nulliparous ($P = .079$), remaining after all adjustments ($P = .058$). Other variables were found not significantly different between both groups (Table 2).

No significant differences were found for EZ width between parous and nulliparous groups, even after adjusting for all variables (Table 2). Median time to events varied between groups, being 17 (95% CI 14-27) years in the parous group versus 21 (95% CI 20-not reached) years in the nulliparous group to reach an EZ width <600 μm; and 9 (95% CI 6-12) years versus 8 (95% CI 5-10) years until EZ width is <7°, respectively (Table 1). Event-free rates were also variable, with 39 (95% CI 28%-48%) parous women retaining an EZ width >15° after 5 years of follow-up, versus 44 (95% CI 29%-58%) of the nulliparous women; and 55 (95% CI 43%-66%) parous women versus 67 (95% CI 50%-79%) nulliparous retaining an EZ width >5° after 10 years of follow-up (Table 1).

Considering only the group of parous women, there were no significant differences associated with a greater number of children and increased risk of RP progression (Table 3). When analyzing number of children as a continuous variable, there was a tendency toward more kids and more severe phenotype (narrower EZ and decreased BCVA); however, this trend was not present when analyzing number of children as a categorical variable (Table 3, Figure 2).

TABLE 3. Multivariate Analysis of Parous Women Taking Into Account Number of Children as a Continuous and Categorical Variable

Metrics	Mothers Subgroup Multivariate Cox Model			
	HR (95% CI) N° Kids	*P* Value	HR (95% CI) >2 kids vs ≤2 kids	*P* Value
Registration status				
Sight impaired	0.94 (0.53-1.66)	.83	0.97 (0.37-2.58)	.96
Severely sight impaired	0.97 (0.7-1.3)	.84	0.65 (0.29-1.43)	.28
Ellipsoid Zone (EZ) Width				
EZ <600 mcm	1.22 (0.89-1.66)	.22	1.13 (0.52-2.46)	.76
EZ ≤15°	0.97 (0.78-1.21)	.8	0.83 (0.51-1.34)	.44
EZ ≤10°	1.06 (0.85-1.33)	.6	0.99 (0.6-1.66)	.98
EZ ≤7°	1.06 (0.83-1.35)	.62	0.88 (0.5-1.55)	.67
EZ ≤5°	1.12 (0.87-1.45)	.22	0.94 (0.5-1.77)	.85
Best-corrected visual acuity (LogMAR)				
BCVA ≥ 0.2	1.16 (0.91-1.49)	.22	1.45 (0.87-2.42)	.15
BCVA ≥ 0.3	1.23 (0.93-1.64)	.15	1.33 (0.73-2.42)	.34
BCVA ≥ 0.7	1.07 (0.79-1.45)	.66	1.07 (0.54-2.09)	.85
BCVA >0.7	1.14 (0.79-1.65)	.48	1.45 (0.61-3.43)	.39

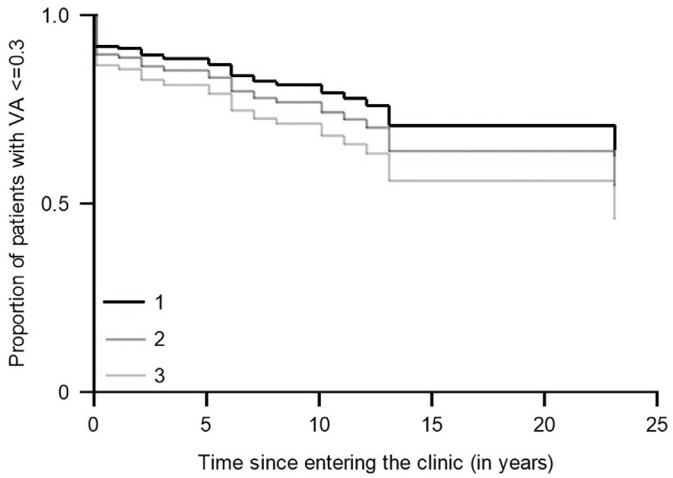

FIGURE 2. Graphic representation of time to BCVA ≤0.3 LogMAR in parous women, divided per number of children had. We see a non-significant trend toward women who had more children reaching worse levels of VA sooner than those with less children. The analysis was adjusted for all confounding variables, including cataract, CMO, age at baseline, and phenotype.

DISCUSSION

Recent studies show that there can be significant sex imbalances in IRD, with *BEST1*-associated macular dystrophy being more common in men than in women, and *EFEMP1*-associated macular dystrophy affecting more women than men.[20] Particularly for *ABCA4*-Stargardt disease, women were found to have a larger proportion of milder alleles than men, establishing a potential association between sex and phenotypic variability.[21,22] This suggests that sex is a potential disease-modifying variable in IRD, with retinal cells being affected by hormonal activity.[23]

There is limited information about the effects of pregnancy on RP, the majority based on patient reports, where up to 10% of patients felt a more rapid disease progression while pregnant, that remained after delivery.[24,25] An old report comments on a slightly depressed scotoma in a patient with a pericentral retinal degeneration, however without genetic testing or a comprehensive ophthalmic history, the baseline diagnosis of this patient is uncertain.[26]

In this study, we found an association between having children and being at increased risk of reaching worse levels of BCVA in women with IRD associated with *USH2A* variants. After adjusting for possible confounders such as phenotype, age at baseline, cataract, and CMO that may

have been left untreated due to pregnancy or lactation, the increased risk in parous women persisted. A non-significant yet consistently increased risk of more severe phenotype was also seen in nearly all events when analyzing number of children as a continuous variable. The fact that the significant change was only seen in BCVA may indicate that this could potentially be secondary to other pregnancy-related ocular complications such as subtle lens or ocular surface changes.[8] EZ width is a classical way of monitoring anatomical disease progression in RP.[27] With variable trends in the data regarding EZ and children, a clear association cannot be made of pregnancy directly affecting RP structural progression.

A possibly similar situation was seen in the inherited progressive condition cystic fibrosis, where pregnancy did not appear to accelerate disease progression per se, but possibly lead to more illness-related visits, pulmonary exacerbations, and decreased quality of life.[28,29] These were thought to be secondary to the physical and emotional challenges of motherhood on disease self-management. It is possible that the outer retinal cells are affected by pregnancy-associated oxidate stress.[30] However, it is also very plausible that parous women with RP may be at risk of having a poorer visual experience secondary to concomitant disorders affecting the visual axis, such as nonsignificant cataracts, dry eye, or corneal thickening, among others.

The study's strengths are the large number of women with *USH2A*-associated IRD, their long follow-up period, and detailed ophthalmic history with multimodal evaluation.

Some of the study limitations include its complex, real-world, retrospective nature with multiple scenarios (eg, some women having cataract surgery versus others being monitored, some having children before their baseline visit at MEH versus others giving birth while being our patients), leading to potential confounding effects. Also, patients could have been registered as SI and SSI elsewhere in the UK by their local eye doctor, and this information could have been missed in MEH medical records. Although ethnicity and socioeconomic status was not collected, the study adequately adjusted for other key variables known to influence the outcome. To mitigate selection bias, we chose the most common gene in MEH to cause RP, *USH2A*, maximizing our chances of having a diverse patient population.

In conclusion, this is the first study to do a large-scale objective analysis of the effects of pregnancy and motherhood in genetically-confirmed women with RP. Women with *USH2A*-associated RP and USH who had children appear to have 3.04 times the risk of reaching BCVA below 20/100 than those who did not have children. A significant association between faster or slower EZ loss and pregnancy was not present in our cohort. It is possible that other factors besides the retinal degeneration are affecting the central vision and causing this increased risk. While additional large-scale studies are necessary to confirm the results of this research, the findings offer valuable insights for women with RP and IRDs who are considering starting a family. These initial results can help inform their decision-making process and guide discussions with healthcare providers.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Malena Daich Varela: Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Memuna Rashid:** Formal analysis. **Andre Lopes:** Writing – review & editing, Supervision. **Michel Michaelides:** Writing – review & editing, Supervision.

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