ORIGINAL RESEARCH ARTICLE

The association between decidual vasculopathy and abnormal uterine artery Doppler measurement

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Abstract

Introduction: Placental syndrome is an umbrella term encompassing the clinical phenotypes of preeclampsia and fetal growth restriction, and is associated with high maternal and neonatal morbidity. In women with placental syndrome, histologicl examination of the uteroplacental unit commonly demonstrates pathological lesions, such as decidual vasculopathy. Decidual vasculopathy are pathological changes in the spiral arteries, which are associated with adverse outcome in preeclampsia and long-term maternal cardiovascular health. The relation between placental syndrome phenotypes and placental pathology has been previously demonstrated; however, the role of uteroplacental Doppler measurements as a link between placental syndrome phenotypes and the underlying placental pathology is still unclear. We hypothesized that decidual vasculopathy is associated with abnormal uteroplacental Doppler profiles and ultrasound placental parameters, independent of clinical phenotype.

Material and Methods: We performed a retrospective analysis of data from a prospective cohort of pregnancies with placental syndrome, as well as cases without hypertensive disease or fetal growth restriction. The study group was divided into women with decidual vasculopathy on histologic analysis of placental specimen and those without the lesions. Outcome parameters included maternal and fetal Dopplers, estimated fetal weight, placental weight and thickness, placental lacunae and abnormal placental calcification.

Results: Compared with the women without the lesions ($n = 91$), the group with decidual vasculopathy ($n = 25$) had a higher mean uterine artery pulsatility index (1.70 vs 0.81, $p < 0.001$) and uterine artery pulsatility index percentile (>p99 vs p67, $p < 0.001$). Decidual vasculopathy was associated with abnormal uterine artery Doppler profile (defined as pulsatility index $p > 95$ and/or bilateral notch) (82%) compared with women without the lesions (33%) (odds ratio [OR] 9.3, 95% CI 2.4–36.0), which remained significant after adjusting for possible confounding factors preeclampsia, tobacco use and gestational age at birth (OR 7.1, 95% CI 1.3–39.1). Decidual vasculopathy was not

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associated with fetal Doppler abnormalities or placental parameters and only modestly so with lower cerebroplacental ratio ($p = 0.036$).

Conclusions: Histologic decidual vasculopathy is associated with abnormal uterine artery Doppler, independent of clinical phenotype during pregnancy.

1 | INTRODUCTION

An adequate placental perfusion, effectuated by an optimal uteroplacental circulation, is mandatory for successful pregnancy. The etiology of the clinical phenotypes of placental syndrome (PS), eg preeclampsia (PE) and/or fetal growth restriction (FGR), is thought to be linked to absent or defective spiral artery remodeling in the placental bed. Typical histopathologic lesions that have been reported in PE and FGR include infarction, villous hypermaturity and decidual vasculopathy (DV) of the spiral arteries.[1,2] DV is a collective term for different subtypes of vascular changes, including fibrinoid necrosis within the walls of non-remodeled vessels—with non-mandatory additional characteristics of foam cell infiltration, perivascular inflammatory cells, and/or thrombosis—and mural hypertrophy of the vessel walls.[3] The precise cause of DV remains unclear; however, defective spiral artery remodeling inevitably leads to fragile maternal arteries that are consequently more prone to develop DV, especially in the presence of other maternal risk factors, such as cardiovascular and cardiometabolic risk factors or thrombophilia.[3] The finding of DV on histologic examination of placental specimens is associated with placental infarction and accelerated villous maturity as well as adverse maternal and neonatal outcome.[3] Moreover, in women with a history of PE, those with DV demonstrated circulatory alterations, potentially elevating their already increased long-term cardiovascular risk, compared with women without the lesions.[4]

Histologic examination can diagnose uteroplacental malperfusion lesions postpartum, but this provides retrospective information which does not aid antepartum clinical decision-making. Therefore, there is potential benefit in the development of predictive markers for these lesions. Abnormalities in placental appearance on ultrasound, namely placental thickness, lacunas and abnormal calcification, have been related to maternal and neonatal complications and/or postpartum placental pathology.[5,6] Additionally, studies have shown that abnormal uterine artery (UtA) Doppler measurements, reflecting a reduced placental perfusion, are associated with an increased risk on developing PS.[7] However, the predictive value of UtA for PS is limited, possibly due to the great heterogeneity in clinical phenotypes of PS and the lack of consensus in definitions pertaining to placental pathology. Moreover, not all clinical phenotypes of PS are consistently associated with reduced placental perfusion (eg late-onset PE). Therefore, we aimed to investigate the association of DV, as a marker for reduced placental perfusion, with uteroplacental

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Key message

Histologic decidual vasculopathy is associated with abnormal uterine artery Doppler, independent of clinical phenotype during pregnancy.

Doppler profiles and ultrasound placental parameters, independent of clinical phenotype. We speculate that the pathological changes of maternal spiral arteries characteristic of DV could lead to dysfunctional blood flow in the uteroplacental unit, reflected by an increased UtA pulsatility index (PI) or the presence of bilateral notches, as well as abnormal ultrasound placental parameters. We hypothesize that there is an association of abnormal uteroplacental Doppler profile and placental ultrasound parameters with the presence of DV upon postpartum histologic examination of placental specimen, regardless of the clinical phenotype during pregnancy.

2 | MATERIAL AND METHODS

2.1 | Study population

In this study we performed a retrospective analysis of data from a prospective cohort of pregnancies collected between 2015 and 2019 at the Maastricht University Medical Centre. Patients were included when they fulfilled the following inclusion criteria: (1) singleton pregnancies with available histology of the placenta, (2) age >18 years, (3) able to speak or understand the Dutch language in order to give informed consent. Fetal anomalies were excluded because of their possible association with placental pathology. Furthermore, we excluded women with preexisting (diagnosed before 20 weeks of gestation) hypertension.

The cohort consisted of women with PS ($n = 19$ PE without FGR; $n = 48$ FGR without PE; $n = 14$ PE with FGR) as well as cases without PS ($n = 33$). PS was defined as FGR and/or PE, developing after 20 weeks of gestation. PE was defined as a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg associated with proteinuria (protein-to-creatinine ratio of ≥30 mg/mol). FGR was defined as an estimated fetal weight <10th percentile (calculated using the Hadlock formula) or abdominal circumference <10th percentile, measured by abdominal ultrasound. The co-occurrence

of PE and FGR was defined as the presence of both PE and FGR diagnosed at time of inclusion. The cases without PS were pregnant women who were managed at Maastricht University Medical Centre for various obstetric indications and had a normotensive, uneventful pregnancy with a normally growing fetus.

Women were divided in two groups: those with and those without DV. DV was defined as the presence of fibrinoid necrosis on histologic examination of placental specimen.[3] Clinical parameters were recorded from electronic records and included body mass index, maternal age, ethnicity, nulliparity, tobacco use, clinical outcome (uncomplicated, PE, FGR or PE with FGR), gestational age at delivery, neonatal birthweight in grams and percentile, 5-min APGAR score <7, arterial umbilical artery pH, and Neonatal Intensive Care Unit admission.

2.2 | Histologic samples

After delivery, the placentas were fixed for at least 48 h in 4% buffered formalin. Umbilical cord and membranes were inspected, the cord length was measured, and afterwards both were removed prior to being weighed, as depicted by the standard hospital protocol. Placental sampling was done in accordance with the Amsterdam Placental Workshop Group Statement[8]: Cross-sections from the maternal and fetal side of the umbilical cord, a minimum of two extraplacental membrane rolls (one from the rupture edge and one extending to the placental margin), and a minimum of three full-thickness sections of normal placental parenchyma were sampled. DV was defined as the presence of fibrinoid necrosis in unremodeled spiral arteries, with or without foam cells, perivascular lymphocytic infiltration or thrombosis.[3] A reviewer (J.dN.T.), blinded for the subjects' clinical outcome, analyzed histologic slides, documenting individual morphological characteristics of DV as performed elsewhere.[6] In addition, in an analysis of interobserver error, a second reviewer (C.S.-R.), who was also blinded for clinical outcome, reanalyzed 101 cases, with an 84% match for the presence of DV.

2.3 | Ultrasound measurements

Doppler measurements were obtained as close as possible to delivery. Transabdominal Doppler velocimetry was performed by experienced sonographers using a 4-8 MHz abdominal transducer (VolusonS10, GE Healthcare). Quantification of the uterine and umbilical flow velocity waveforms was conducted by measuring three or more consecutive waveforms with an angle of insonation as close to 0° as possible. Subsequently, PI was calculated with its corresponding percentile corrected for gestational age. The left and right UtA were identified using color flow imaging at the crossover point with the external iliac artery and placing the Doppler gate just above this point.[9] Mean UtA-PI was calculated as the average PI of the right and left artery. A single known artery measurement was required for analysis. Umbilical artery-PI was calculated from measurements in a free-floating cord loop.[9] Middle cerebral artery Dopplers were

obtained in an axial section of the brain, revealing the circle of Willis, at the proximal third of the middle cerebral artery, close to its origin in the internal carotid artery.[9] All measurements were obtained with ASTRAIA OBSTETRICS software (version 1.25.12). An UtA- or umbilical artery-PI >p95 and/or the presence of UtA bilateral diastolic notch was considered abnormal. Cerebroplacental ratio was calculated (middle cerebral artery-PI divided by umbilical artery-PI), with a cerebroplacental ratio percentile <p5 being considered abnormal.

Placental measurements were obtained in grayscale mode. The placenta was screened for the presence of placental focal lucencies (placental lakes) and placental calcifications, and placental thickness was measured. Placental thickness (in mm) was measured underneath the umbilical cord insertion, perpendicular to the uterine wall. Placental lakes were defined as intraparenchymal, subchorional or an echogenic cystic lesion and there were no restrictions on the size of the lakes. For the purpose of this study, we only graded the placental lakes as "present" or "absent." Placental calcifications were graded by the Grannum classification.[10] The presence of "grade 3" calcifications was defined as "abnormal" throughout gestation.

2.4 | Statistical analyses

Statistical analysis was carried out using IBM SPSS Statistics for Windows (v25; IBM Corp.) Continuous variables were analyzed for normal distribution. For dichotomous variables, differences between groups were compared using Chi-square test or Fisher's exact test. For continuous variables Mann–Whitney test or independent samples t-test were used. Odds ratios were calculated using binary logistic regression. Continuous outcomes were expressed as median with interquartile range or mean with standard deviation, for non-parametric variables or parametric variables, respectively, and dichotomous outcomes were expressed as percentages. A two-sided p-value ≤0.05 was considered statistically significant.

2.5 | Ethical approval

Ethical approval for this study was given by the Ethics Committee of the Maastricht University Medical Centre (METC 15–4-026) on February 18, 2016.

3 | RESULTS

A total of 116 pregnancies were included in this study. The overall prevalence of DV was 22%. As presented in Table 1, maternal characteristics between the two study groups were comparable, except for tobacco use (DV+ 0% vs DV− 21%, $p = 0.012$). Analyzing clinical outcome, in the DV+ group, 17% had an uncomplicated outcome, 25% PE without FGR, 29% FGR without PE, and 29% PE and FGR. In the DV− group, 32% of women had an uncomplicated outcome, 14% PE without FGR, 45% FGR, and 8% PE and FGR. Comparing

TABLE 1 Background parameters

	Decidual vasculopathy+ group (n = 25)	Decidual vasculopathy− group (n = 91)	p-value
Maternal parameters			
Body mass index (kg/m^2)	24.7 (± 5.4)	23.9 (± 4.2)	0.498[a]
Age (years)	31 (28–36)	32 (29–33)	0.440
Ethnicity			0.069[b]
Caucasian	79% (19/24)	91% (83/91)	
Negroid	0% (0/24)	2% (2/91)	
Asian	13% (3/24)	1% (1/91)	
Mediterranean	8% (2/24)	4% (4/91)	
Other	0% (0/24)	1% (1/91)	
Nulliparous	70% (16/23)	61% (49/80)	0.466
Tobacco use	**0% (0/23)**	**21% (19/90)**	**0.012[b]**
History of preeclampsia[c]	14% (1/7)	19% (7/37)	0.771
History of fetal growth restriction[c]	14% (1/7)	27% (10/37)	0.475
Prevalence of clinical outcomes			**0.022 [b]**
Uncomplicated (no hypertension or fetal growth restriction)	17% (4/24)	32% (29/90)	
Preeclampsia without fetal growth restriction	25% (6/24)	14% (13/90)	0.086[d]
Fetal growth restriction without preeclampsia	29% (7/24)	45% (41/90)	0.751[d]
Preeclampsia and fetal growth restriction	**29% (7/24)**	**8% (7/90)**	**0.005[d]**
Neonatal parameters			
Gestational age at birth (days)	**238 (204–256)**	**260 (239–267)**	**0.002**
Birthweight (g)	**1385 (922–2726)**	**2365 (1650–2960)**	**0.026**
Birthweight percentile	14 (7–40)	19 (8–44)	0.878
5 min APGAR <7	29% (7/24)	29% (26/91)	0.954
Arterial umbilical artery pH	7.23 (± 0.08)	7.24 (± 0.07)	0.711[a]
Neonatal intensive Care Unit admission	**63% (15/24)**	**32% (28/89)**	**0.005**

All continuous values: median (interquartile range), using Mann–Whitney test, except for [a] .

All categorical values: percentage, Chi square, except for [b].

Significant results are in bold.

[a] Mean (standard deviation), using independent samples *t*-test.

[b]Fisher's exact test.

[c]Percentage of multiparous women.

[d]Compared with control.

different PS phenotypes with the uncomplicated outcome showed a significantly higher percentage of PE with FGR in the DV+ group (*p* = 0.005). Gestational age at birth was shorter for the DV+ group than for the DV-group (238 vs 260 days, *p* = 0.002). Additionally, the neonatal birthweight, but not birthweight percentile, was lower in the DV group (1385 g vs 2365 g, *p* = 0.026) and there was a higher rate of Neonatal Intensive Care Unit admission in the DV group (63% vs 32%, *p* = 0.005) than in the DV− group.

For ultrasound parameters (Table 2), there was a higher prevalence of abnormal maternal Doppler profiles in the DV+ group than in the DV− group. UtA-PI and the UtA-PI percentile were higher in the DV+ group than in the DV− group (respectively UtA-PI 1.70 vs 0.81, *p* < 0.001; UtA-PI percentile *p* > 99 vs p67, *p* < 0.001). There was a higher percentage of UtA-PI >p95 (DV+ 83% vs DV− 30%, *p* < 0.001) and bilateral notch of the UtA (DV+ 61% vs DV− 25%, *p* = 0.003) in the DV group. Additionally, a higher percentage of abnormal UtA Dopplers and higher uteroplacental ratio were found in the DV+ group (82% vs 33%, *P* ≤ 0.001; 1.48 vs 0.82, *p* < 0.001). The middle cerebral artery-PI was lower in the DV+ group (DV+ 1.45 vs DV− 1.70, *p* = 0.044). There was no difference in other fetal Doppler

TABLE 2 Ultrasound parameters

	Decidual vasculopathy+ group (n = 25)	Decidual vasculopathy− group (n = 91)	p-value
Gestational age at measurement (days)	211 (193–244)	218 (204–245)	0.416
Fetal weight parameters			
Estimated fetal weight (g)	1351 (755–2175)	1423 (949–2063)	0.608
Estimated fetal weight percentile	6 (1–35)	9 (1–37)	0.733
Maternal Doppler parameters			
Mean uterine artery pulsatility index	**1.70 (1.28–1.91)**	**0.81 (0.65–1.33)**	**<0.001**
Mean uterine artery pulsatility index percentile	**100 (99–100)**	**67 (21–98)**	**<0.001**
Abnormal uterine artery pulsatility index[a]	**83% (15/18)**	**30% (20/67)**	**<0.001**
Bilateral notch uterine artery	**61% (11/18)**	**25% (16/65)**	**0.003**
Abnormal uterine artery Doppler profile[b]	**82% (14/17)**	**33% (21/63)**	**<0.001**
Fetal Doppler parameters			
Umbilical artery pulsatility index	1.09 (0.93–1.45)	1.04 (0.94–1.29)	0.561
Umbilical artery pulsatility index percentile	81 (34–95)	73 (40–93)	0.664
Middle cerebral artery pulsatility index	**1.45 (1.08–1.81)**	**1.70 (1.39–1.99)**	**0.044**
Middle cerebral artery peak systolic velocity	37 (30–49)	39 (28–45)	0.778
Cerebroplacental ratio	**1.12 (1.01–1.57)**	**1.47 (1.22–1.89)**	**0.055**
Cerebroplacental ratio percentile	**1 (0.2–9.9)**	**5.7 (1.0–30.6)**	**0.036**
Placental parameters			
Abnormal classification[c]	22% (5/23)	23% (18/77)	0.870
Placental lakes	74% (17/23)	60% (51/85)	0.220
Placental weight (g)	282 (205–429)	334 (264–453)	0.319
Placental weight percentile	10 (9–67)	9 (9–36)	0.288
Placental thickness (mm)	29 (24–37)	31 (27–37)	0.354

All continuous values: median Mann–Whitney test.

All categorical values: percentage, Chi square.

Significant results are in bold.

[a]Uterine artery pulsatility index >p95.

[b]Uterine artery pulsatility index >p95 and/or bilateral notch.

[c]Grade 3 (Grannum-classification).

TABLE 3 Abnormal maternal Dopplers: clinical groups

	Decidual vascolopathy+ group (n = 17)	Decidual vascolopathy− group (n = 62)	p-value
Clinical groups			
Uncomplicated (no hypertension or fetal growth restriction)	67% (2/3)	21% (3/14)	0.119
Preeclampsia without fetal growth restriction	67% (2/3)	30% (3/10)	0.252
Fetal growth restriction without preeclampsia	**100% (4/4)**	**36% (11/31)**	**0.026**[a]
Preeclampsia and fetal growth restriction	**86% (6/7)**	**57% (4/7)**	**0.280**[a]

All categorical values: percentage, Chi square, except for [a].

Significant results are in bold.

[a]Fisher's exact test.

measurements or in estimated fetal weight or estimated fetal weight percentile. Furthermore, there was no difference in postpartum placental weight in grams or percentile, and ultrasound parameters of placental thickness, the incidence of abnormal placental calcifications or the presence of placental lakes between the two groups.

When stratifying for different clinical categories (Table 3), DV was not significantly associated with abnormal UtA Doppler, except

for the group of FGR without PE (DV+ 100% vs DV− 36%, $p = 0.026$); the strength of the analysis was limited due to the small number of cases per group.

We analyzed the association of abnormal UtA Doppler with DV. The odds ratio of abnormal UtA Doppler for DV was 9.3 (95% CI 2.4–36.0, $p = 0.001$). When adjusted for PE, FGR without PE, tobacco use and gestational age at birth, the odds ratio (OR) was 7.0 (95% CI 1.3–38.6, $p = 0.025$).

4 | DISCUSSION

In this retrospective study, we studied the association between ultrasound measurements and the presence of DV in a group of pregnant women with diverse clinical outcomes. Our main finding was the strong association between abnormal uterine artery Doppler measurements and DV, even after correcting for confounding factors and irrespective of the clinical phenotype. Additionally, pregnancies with DV showed a higher mean PI percentile of the UtA and a higher number of cases with abnormal Doppler profile of this artery (bilateral notch or PI mean centile >p95).

Interestingly, in this study, there was a significantly higher prevalence of tobacco use in the group of women without DV. If this finding is confirmed it could have potential implications for the pathophysiologic process underlying the lesions. Previous studies have shown a reduced risk of PE for tobacco-smoking women; however, the underlying mechanism has yet to be elucidated. There is some evidence that this reduction is not due to nicotine use itself but rather the combustion products, with a possible role of carbon monoxide as a vascular protective agent.[11] It would be interesting to explore this opposing association between smoking and DV, as well as its potential underlying pathophysiologic mechanisms in future research.

Abnormal uterine artery Doppler profile is thought to be associated with suboptimal placentation. In an attempt to assess the risk of developing placental syndrome, these Doppler measurements were incorporated in several management and predictive models. However, its predictive value for clinical outcome is limited, presumably due to the heterogeneous nature of the placental syndrome.[12–14] The clinical presentation of preeclampsia is highly variable, leading to the proposition of different subtypes of the disease, such as early and late, the former of which is more strongly associated with uteroplacental pathology.[15] Theoretically, (partial) failure of the spiral arteries, which anatomically are downstream of the uterine artery, to adapt to pregnancy, causes its abnormal Doppler profile.[16] However, recent studies have suggested that the other uterine vessels, including arcuate arteries, placental bed arterio-venous anastomoses and radial arteries, play a more significant role in uterine artery Doppler ultrasound than previously thought.[17] It has been hypothesized that, in turn, DV lesions impact uteroplacental blood flow, and subsequently uterine artery Dopplers.[16] To our knowledge, we are the first to investigate the association of Doppler profile and placental ultrasound parameters with DV in a diverse clinical group.

Historically, DV has been described in placental specimens of women with a variety of clinical outcomes, but with a higher prevalence in women with placental syndrome, or with comorbidities predisposing to vascular pathology, such as diabetes mellitus or autoimmune disease.[18,19] In our study, the outcome of PE with FGR had a significant prevalence in the DV group compared with the uncomplicated outcome group. In preeclampsia, DV has been associated with adverse clinical outcome.[3] Although the main focus of our current study was not maternal or neonatal outcomes, our results showed that pregnancies with DV had a shorter gestational age at birth, as well as a higher percentage of Neonatal Intensive Care admission. Lastly, our previous research has shown the association of DV with circulatory alterations, suggesting reduced venous reserves and elevated arterial tone in women with a history of PE, possibly placing them at an even higher risk of developing cardiovascular complications than their counterparts not containing the lesions.[4]

The finding of an abnormal uterine artery profile within the DV group has two potential implications. We argue that the association of uterine Doppler profile with the presence of the lesions could potentially be used to build a predictive model for DV, especially when combined with other potential indicators, such as angiogenic factors. This model and the association of additional (bio)markers with DV could be explored in future studies. A sufficiently robust model could be used to identify (asymptomatic) pregnant women with uteroplacental vasculopathy, regardless of their clinical phenotype at the time of measurement, which could indicate an elevation of their risk status and concurrent adjustment of their management during pregnancy.

Secondly, the predictive model could be used to identify women with an indication for histologic examination of the placenta postpartum. When the lesions are confirmed, this would create an opportunity for affected women to benefit from a more intensive cardiovascular screening program, initiated earlier in life than the current standard. These women would likely benefit from a thorough analysis of relevant risk factors in the postpartum period, followed by long term check-ups.

A strength of this study is that both reviewers were blinded for clinical outcome and that the histologic samples were revised. A limitation of this study is that we used a cross-sectional measurement of estimated fetal weight or abdominal circumference as our definition of FGR, thus potentially including fetuses with limited growth due to non-placental causes (eg genetic or infectious). However, we theorize that this did not dilute our findings, as we aimed to study the association of DV with Doppler measurements independent of clinical groups. Additionally, when we analyzed our findings using the parameter of small-for-gestational age (postnatal birthweight percentile ≤10), instead of FGR, our results were similar (adjusted OR of DV for abnormal UtA 7.6, 95% CI 1.3–43.2).

5 | CONCLUSION

This study is the first to investigate the association between the presence of DV and antepartum UtA Doppler measurements. The

association of abnormal maternal Doppler profile with DV could potentially aid in clinical decision making, including the intensity of maternal check-ups during pregnancy and the indication for histologic analyses of the placenta postpartum, specifically to identify women at higher risk of developing cardiovascular comorbidities later in life. This study emphasizes the need for incorporating ultrasound measurements, such as uterine Doppler profile, in routine antenatal care. Moreover, it raises the question of whether ostensibly asymptomatic woman and fetuses could benefit from screening for abnormal Doppler profile. Our results indicate the importance of maintaining a broadened perspective in screening and care of pregnant women, and the risk of tunnel vision when focusing only on specific clinical groups. We therefore advocate an approach directed at the detection of underlying pathology in pregnant women. We believe the potential benefit of this method will not be limited to improving antenatal care, but could also guide physicians in the long-term care of women with elevated cardiovascular risk.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All of the authors have made vital contributions to and have critically revised and approved the manuscript. DS, VS, JdNT. and AvH processed the study data. DS and VS performed all data analysis and took the lead in composing the manuscript. CS-R performed the histologic revision. JdNT performed the histologic analysis; MS and SA-N contributed to the design of the study, to the analysis of the results and to the writing of the manuscript.

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