Final version published as Christians, J.K. and Grynspan, D. (2019) Placental villous hypermaturation is associated with improved neonatal outcomes. *Placenta*. DOI: 10.3109/14767058.2012.746297

Placental villous hypermaturation is associated with improved neonatal outcomes

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Abstract

Introduction: Accelerated placental maturation is considered a sign of maternal vascular malperfusion, and is often interpreted as an adaptive, compensatory response by the placenta. We tested this interpretation by comparing outcomes in pregnancies with and without accelerated maturation.

Methods: Using data from the National Collaborative Perinatal Project, we categorized preterm placentas (24 - 34 weeks, inclusive; 2525 births) by whether they showed placental villous hypermaturation (PVH), i.e., had the appearance of a placenta of 37 weeks or over upon microscopic examination. We assessed whether PVH was associated with maternal race, maternal BMI, fetal sex, type of preterm birth, preeclampsia, signs of infection or inflammation or placental abruption. We also assessed whether placentas showing PVH were associated with improved outcomes in terms of survival, Apgar score, or oxygen use.

Results: PVH was more common in preeclamptic pregnancies and less common in pregnancies complicated by placental abruption or showing signs of placental infection or inflammation. Adjusting for potentially confounding factors, PVH was associated with reduced odds of fetal death, death between birth and 120 days of age, low Apgar scores and oxygen use. PVH was also associated with higher birthweights for gestational age. When correcting for the effect of birthweight, the association between PVH and reduced fetal and neonatal death remained significant.

Discussion: Accelerated placental maturation, as manifested by PVH, is associated with improved outcomes. Our work therefore supports the hypothesis that accelerated maturation is a compensatory response by the placenta to improve its transport capacity in specific pregnancy complications.

Keywords: accelerated maturation; compensation; hypermaturation; pathology; preterm; outcome

1. Introduction

The placenta must adjust its growth, morphology and function in response to nutrient and oxygen availability [1]. One potential adjustment is to increase its rate of maturation, which is considered an adaptive response to certain patterns of hypoxia [2,3]. Specifically, accelerated maturation is viewed as a sign of maternal vascular malperfusion [4–6], e.g., resulting from impaired spiral artery remodeling and blood flow, and often associated with preeclampsia [2,3,6–9]. There is variability in the definition of villous maturity [10], but accelerated placental maturation (or accelerated villous maturation) generally includes aspects of improved efficiency in terms of surface area and diffusion distances (e.g., a lack of Langhans layer, the layer of cytotrophoblast under the syncytiotrophoblast, and crowding of fetal capillaries within villi) [11]. However, accelerated maturation also includes decreased villous branching and aspects of age-related parenchymal damage such as increased presence of fibrin and an increase in syncytial knots [5,12], which are normally less frequent preterm [13]. Furthermore, some authors distinguish between heterogenous hypermaturity (where a preterm placenta has the morphology of a term placenta) and homogenous hypermaturity, which is considered abnormal regardless of gestational age [2,3]. To complicate matters further, placental maturity is also assessed by ultrasound [14] reflecting in part calcification [15,16], although placentas assessed to be more mature by ultrasound have increased diffusion capacity due to a thinner villous membrane and possibly to increased surface area [17].

Although accelerated placental maturation is a sign of placental pathology, it is viewed as an adaptive, compensatory response [2,18]. The objective of the present study was to test this interpretation. If accelerated placental maturation is a compensatory response, we predicted that preterm placentas showing accelerated maturation would be associated with improved outcomes

compared with placentas from similar pregnancies that do not show acceleration. To account for potentially confounding variables, we first sought to identify maternal, fetal and clinical characteristics that were associated with acceleration. Specifically, we examined whether acceleration was associated with maternal race and/or BMI, since both of these factors are associated with the risk of preeclampsia and placental pathology [19–22]. We also examined fetal sex as this influences the response to adverse conditions [23]. Finally, we assessed the association of accelerated placental maturation with preeclampsia, placental abruption, signs of infection and category of prematurity. We tested our predictions using data from the National Collaborative Perinatal Project.

2. Methods

The National Collaborative Perinatal Project (NCPP) has been described elsewhere [24], and its data are publicly available (https://catalog.archives.gov/id/606622). Accelerated villous maturation is difficult to recognize at term [2,12,25] and so we focused on preterm births (24 - 34 weeks, inclusive). Our lower limit for gestational age was based on the limit of viability [26], and we excluded late preterm births (35 - 36 weeks) to reduce the potential for error in the assessment of maturity [25]. We used assessments of the apparent maturity of the placenta that were available in the database. These assessments were based upon microscopic examination, and classified appearance as 36 weeks or less vs. 37 weeks or over (Table 1) [11]. In this dataset the actual gestational age was calculated based on the last menstrual period to the nearest week. Given the differing definitions of accelerated placental maturation (described above), we use the term placental villous hypermaturation (PVH) following Morgan et al. to refer to preterm placentas with the morphological appearance of term placentas [18]. We used only singleton

pregnancies where offspring sex was assigned male or female; fetal and neonatal deaths were included. Where a woman had more than one pregnancy included in the study, we included only her first study pregnancy, and cases were not excluded on the basis of maternal health conditions or congenital abnormalities. For 91% of these births, maternal race was categorized as white or black, and so analyses were restricted to these two races. These criteria yielded 3030 eligible births, for which assessment of PVH was available for 2525. Birthweights were corrected for maternal race, offspring sex and gestational age using a general linear model, after first removing the top and bottom 0.5% of raw birthweights to objectively exclude biologically implausible values [27]. To assess placental efficiency, we calculated the residuals of the linear regression of corrected birthweight on placental weight (corrected for maternal race, offspring sex and gestational age) using the RESIDUAL statement of proc GLM (SAS, Version 9.4) [27].

Preterm births were categorized as (1) induced labour and/or caesarian delivery as a result of medical indication, (2) spontaneous labour with intact membranes, or (3) preterm premature rupture of membranes (i.e., rupture of membranes occurred before labour) [28,29]. Placentas were categorized as showing signs of infection or inflammation if one or more of the following was observed: neutrophilic infiltration of the amnion of membrane roll, of the amnion of placental surface, of the chorion of membrane roll, or of umbilical vein. Maternal body mass index (BMI) was categorized as underweight (< 18.5), normal (18.5-25), overweight (>25 – 30) or obese (> 30).

To identify factors associated with PVH, we performed logistic regression investigating whether the odds of PVH were associated with maternal race, maternal BMI, fetal sex, category of preterm birth, preeclampsia (yes/no), signs of infection or inflammation (yes/no) and placental abruption (yes/no) (proc LOGISTIC, SAS, Version 9.4). To assess whether placentas showing

PVH were associated with improved outcomes, we used multinomial logistic regression to test whether the odds of survival (categorized as fetal death, death between birth and 120 days of age, or survival past 120 days) were associated with PVH, adjusting for other terms associated with PVH from the previous analysis. Similarly, multinomial logistic regression was used to test whether the odds of a favorable Apgar score at 1 and 5 minutes (categorized as 0-3, 4-6, or 7-10, where larger numbers are better), or the odds of oxygen being used in the nursery (yes/no), were associated with PVH, adjusting for other terms. Corrected birthweight and placental efficiency were analysed by general linear model (proc GLM, SAS, Version 9.4), including other terms significantly associated with PVH.

3. Results

Adjusting for other terms in the model, PVH was more common in black women and preeclamptic pregnancies (Table 2). It was less common in women who were underweight prior to pregnancy and in pregnancies complicated by placental abruption or associated with placental infection or inflammation (Table 2). Fetal sex and category of prematurity were not significantly associated with PVH (Table 2).

The odds of fetal death, and the odds of death between birth and 120 days of age, were lower in pregnancies showing PVH, adjusting for gestational age, maternal race, maternal BMI, presence of preeclampsia, signs of infection or inflammation and presence of abruption (Table 3). Similarly, the odds of lower Apgar scores at 1 and 5 minutes, and the odds of oxygen being used in the nursery, were also lower in pregnancies showing PVH, adjusting for the same variables (Table 3).

Corrected birthweight was higher in pregnancies showing PVH (with PVH: 2419 ± 38 g; without PVH: 1747 ± 37, $P < 0.0001$), adjusting for maternal race, maternal BMI, presence of preeclampsia, signs of infection or inflammation and presence of abruption (birthweight had already been adjusted for gestational age, and so this term was not included in the model). Placental efficiency was assessed using residuals of the regression of birthweight on placental weight [27] to quantify whether newborns were small or large relative to their placenta. Efficiency was higher in pregnancies showing PVH (with PVH: 2 ± 29 g lower birthweight than expected for placental weight; without PVH: 287 ± 29 g lower birthweight than expected for placental weight, $P < 0.0001$), adjusting for covariates.

To assess whether the reduced odds of adverse perinatal outcomes were due to increases in birthweight, we repeated the multinomial logistic regression, adjusting for corrected birthweight in addition to the variables described above. Pregnancies showing PVH had reduced odds of both fetal and neonatal death and lower Apgar scores at 1 minute, although the latter was marginally non-significant (Table 3). When adjusting for birthweight, PVH was not associated with better Apgar scores at 5 minutes or whether oxygen was used in the nursery (Table 3).

To examine whether the results were an artifact of the multinomial logistic regression, we analysed a more restricted dataset including the most common combination of variables: black race with no placental abruption and no preeclampsia. We also restricted this analysis to a narrower range of gestational ages, between 28 and 30 weeks (inclusive), to avoid potential confounding of pathologies with gestational age [30]. Among pregnancies showing no signs of placental infection or inflammation, those with PVH had reduced odds of fetal and neonatal death, lower Apgar scores at 1 minute, and oxygen use in the nursery (Table 4). Among pregnancies showing signs of placental infection or inflammation, PVH was associated with

reduced odds of fetal death, and tended to show reduced odds of lower Apgar scores at 1 minute, although this result was marginally non-significant (Table 4). However, none of these effects were significant when adjusting for birthweight (data not shown).

4. Discussion

Clinically, accelerated maturation is viewed as a sign of utero-placental insufficiency and this interpretation is supported by experimental evidence from a non-human primate model [31]. The term "accelerated placental maturation" is used to describe a variety of related phenotypes, and in the present study we examined placental villous hypermaturation (PVH [18]) where a preterm placenta has the morphological appearance of a term placenta. This hypermaturation is considered to be an adaptive, compensatory response [2,18], and in the present study we show for the first time that PVH is indeed associated with improved outcomes. We observed this association when controlling for gestational age, maternal race, BMI and pregnancy complications, and also when analyzing a restricted dataset including only pregnancies with similar characteristics. PVH was also associated with higher birthweight and placental efficiency, and so may improve outcomes in part by improving fetal growth. However, these associations do not establish that PVH improves fetal growth. Furthermore, in some analyses, PVH was associated with better outcomes even when adjusting for birthweight, suggesting mechanisms not dependent on birthweight. PVH was also associated with reduced odds of oxygen use in the nursery, perhaps reflecting improved fetal lung development. This suggests that there may be an association between accelerated placental maturation and accelerated fetal maturation, whereby both the placenta and fetus receive signals indicating that the pregnancy may not progress to term.

The association of PVH with improved outcomes raises the question of why more preterm placentas did not show acceleration. PVH was less common in women who were underweight pre-pregnancy, suggesting a potential nutritional constraint on accelerating development. Alternatively, placentas not showing PVH may have not received signals indicating that preterm birth was likely. Our results are consistent with the model whereby there are two general categories of preterm births: those due to impaired placental development, and those due to intrauterine inflammation [30,32]. In our study, preeclampsia was associated with higher odds of PVH, whereas infection or inflammation and abruption were associated with lower odds of PVH. Thus, placentas in preeclamptic pregnancies, associated with abnormal placentation, may have received chronic signals indicating pathology and the need to accelerate development. In contrast, in pregnancies with infection, inflammation and abruption, the development of pathology may have been more recent, giving the placenta less time to adjust. Consistent with our findings, PVH was previously found to be more common in preeclamptic pregnancies than in those with acute chorioamnionitis [18], and IUGR pregnancies with hypertensive disease were more likely to show increased maturation than normotensive IUGR pregnancies [8]. Similarly, accelerated villous maturation was previously found to be more prevalent in indicated preterm births than in spontaneous preterm births; the latter being associated with inflammatory lesions [6]. A limitation of our study is that our histological criteria for assessing inflammation and infection may have missed some cases of infection. If these false negatives were less likely to show PVH, then the association between a lack of PVH and poor outcomes could be due to shared association with infection, rather than a beneficial effect of PVH. However, in a restricted dataset including only pregnancies with signs of inflammation or

infection (i.e., not subject to the potential issue of false negatives), pregnancies associated with PVH showed reduced odds of fetal death.

Our work provides empirical support for the hypothesis that accelerated maturation is a compensatory response by the placenta in chronic adverse conditions such as maternal vascular malperfusion. Accelerated maturation includes morphological changes (lack of the Langhans layer and crowding of fetal capillaries) that would be expected to reduce diffusion distance and thereby increase transport and diffusion.

Declarations of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We thank the U.S. National Archives for making the National Collaborative Perinatal Project data freely available.

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Table 1. Traits associated with greater maturity that were used to categorize the appearance of a preterm placenta as 36 weeks or less vs. 37 weeks or over [11]. The present study used assessments performed as part of the National Collaborative Perinatal Project and did not reassess maturity.

Presence of fibrin under the chorionic plate
Presence of cysts on the cut surfaces
Lack of Langhans layer
Relative uniformity of villous size
Crowded fetal capillaries within villi
Increased frequency of syncytial knots

322 Table 2. Factors associated with placental villous hypermaturation (PVH).

		PVH		Odds ratio[1]	P-value	Adjusted odds ratio[2]	P-value
		Yes # (%)	No # (%)	(95% CI)		(95% CI)	
Maternal race	White	335 (51.5)	315 (48.5)		<0.0001		<0.0001
	Black	1309 (69.8)	566 (30.2)	2.2 (1.8-2.6)		1.9 (1.5-2.3)	
Maternal BMI	Underweight	272 (55.1)	222 (44.9)		<0.0001		0.0002
	Normal	1066 (66.9)	528 (33.1)	1.6 (1.3-2.0)		1.6 (1.3-2.0)	
	Overweight	213 (70.1)	91 (29.9)	1.9 (1.4-2.6)		1.8 (1.3-2.5)	
	Obese	93 (69.9)	40 (30.1)	1.9 (1.3-2.9)		1.9 (1.1-3.0)	
Fetal sex	Male	865 (64.8)	470 (35.2)		0.73		0.41
	Female	779 (65.5)	411 (34.5)	1.0 (0.9-1.2)		1.1 (0.9-1.3)	
Category of prematurity	Induced	102 (57.6)	75 (42.4)		0.06		0.42
	Spontaneous labour	1309 (66.3)	666 (33.7)	1.4 (1.1-2.0)		1.3 (0.9-1.9)	
	PPROM	221 (67.2)	108 (32.8)	1.5 (1.0-2.2)		1.4 (0.9-2.1)	
Preeclampsia	No	1218 (63.7)	693 (36.3)		<0.0001		0.0076
	Yes	335 (74.4)	115 (25.6)	1.7 (1.3-2.1)		1.4 (1.1-1.8)	
Infection or inflammation	No	1265 (70.5)	529 (29.5)		<0.0001		0.0001
	Yes	379 (51.9)	352 (48.2)	0.45 (0.38-0.54)		0.48 (0.40-0.59)	

Placental abruption	No	1568 (67.5)	755 (32.5)		<0.0001		<0.0001
	Yes	69 (39.2)	107 (60.8)	0.31 (0.23-0.43)		0.36 (0.25-0.51)	

[1]All odds ratios are calculated as the odds of showing PVH, compared with the first level for each factor, e.g., the odds ratio of showing PVH for a black woman compared to a white woman. [2]Adjusted odds ratios are from logistic regression including all terms in the model simultaneously, as well as gestational age.

330 Table 3. The odds of death, unfavorable Apgar scores, and oxygen use in the nursery in association with PVH.

		PVH		Odds ratio[1]	P-value	Adjusted odds ratio[2]	P-value	Adjusted odds ratio, including birthweight[3]	P-value
		Yes # (%)	No # (%)	(95% CI)				(95% CI)	
Survival	Died prior to birth	34 (2)	158 (18)	0.07 (0.05-0.10)	< 0.0001	0.09 (0.06-0.14)	< 0.0001	0.31 (0.18-0.53)	< 0.0001
	Died between birth and 120 days	69 (4)	216 (25)	0.11 (0.08-0.14)		0.16 (0.12-0.23)		0.54 (0.36-0.79)	
	Survived to 120 days	1541 (94)	506 (58)						
Apgar score at 1 minute	0-3	126 (9)	194 (31)	0.18 (0.14-0.23)	< 0.0001	0.26 (0.20-0.35)	< 0.0001	0.67 (0.48-0.93)	0.06
	4-6	240 (16)	134 (21)	0.48 (0.38-0.62)		0.55 (0.42-0.71)		0.87 (0.65-1.17)	
	7-10	1103 (75)	297 (48)						
Apgar score at 5 minutes	0-3	51 (3)	126 (20)	0.12 (0.09-0.17)	< 0.0001	0.20 (0.14-0.29)	< 0.0001	0.68 (0.44-1.07)	0.20
	4-6	93 (6)	113 (18)	0.25 (0.18-0.33)		0.33 (0.24-0.45)		0.83 (0.57-1.20)	
	7-10	1363 (90)	405 (63)						

Oxygen used in nursery	Yes	111 (8)	161 (34)	0.16 (0.12-0.21)	< 0.0001	0.22 (0.17-0.30)	< 0.0001	0.78 (0.53-1.16)	0.22
	No	1358 (92)	317 (66)						

[1]All odds ratios are calculated as the odds of the adverse outcome, compared with the most favorable outcome, e.g., the odds ratio of death prior to birth relative to survival to 120 days for a pregnancy showing PVH compared to one without PVH.

[2]Adjusted odds ratios are from multinomial logistic regression including PVH, gestational age, maternal race, maternal BMI, presence of preeclampsia, infection/inflammation, or abruption. Gestational age, maternal race, presence of abruption and infection were significant in all analyses. Presence of preeclampsia was significant in the analysis of survival. Maternal BMI was not significant in any analysis.

[3]Adjusted odds ratios are from multinomial logistic regression as above but also including corrected birthweight. Gestational age, corrected birthweight and maternal race were significant in all analyses. Presence of preeclampsia was significant in the analysis of survival. Signs of infection/ inflammation was significant in analyses of Apgar score at 1 minute and at 5 minutes. Presence of abruption was significant in analyses of survival and Apgar score at 1 minute. Maternal BMI was not significant in any analysis.

Table 4. The odds of death, unfavorable Apgar scores, and oxygen use in the nursery in association with PVH, including only pregnancies of black women with no placental abruption and no preeclampsia delivered between 28 and 30 weeks (inclusive), with or without signs of placental infection or inflammation.

		No signs of infection or inflammation				Signs of infection or inflammation			
		PVH		Adjusted odds ratio[1]	P-value	PVH		Adjusted odds ratio[1]	P-value
		Yes # (%)	No # (%)	(95% CI)		Yes # (%)	No # (%)	(95% CI)	
Survival	Died prior to birth	1 (1)	4 (8)	0.06 (0.01-0.57)	0.003	1 (2)	9 (20)	0.07 (0.01-0.56)	0.01
	Died between birth and 120 days	5 (5)	9 (19)	0.22 (0.07-0.72)		6 (12)	12 (27)	0.33 (0.10-1.06)	
	Survived to 120 days	103 (95)	35 (73)			42 (86)	23 (52)		
Apgar score at 1 minute	0-3	4 (4)	6 (16)	0.20 (0.05-0.77)	0.04	5 (12)	11 (35)	0.24 (0.07-0.84)	0.08
	4-6	14 (14)	8 (21)	0.52 (0.19-1.41)		11 (27)	8 (26)	0.66 (0.21-2.09)	
	7-10	84 (82)	24 (63)			26 (62)	12 (39)		

Apgar score at 5 minutes	0-3	0 (0)	3 (7)	<0.001 (<0.001->999)	0.52	4 (10)	7 (23)	0.30 (0.08-1.22)	0.13
	4-6	5 (5)	5 (12)	0.46 (0.12-1.75)		7 (17)	8 (27)	0.41 (0.12-1.37)	
	7-10	96 (95)	34 (81)			31 (74)	15 (50)		
Oxygen used in nursery	Yes	7 (7)	14 (44)	0.10 (0.04-0.29)	<0.0001	9 (20)	9 (36)	0.46 (0.15-1.38)	0.16
	No	92 (93)	18 (56)			35 (80)	16 (64)		

[1]All odds ratios are calculated as the odds of the adverse outcome, compared with the most favorable outcome, adjusting for gestational age.