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PEDIATRICS

Birth-related retinal hemorrhages in healthy full-term newborns and their relationship to maternal, obstetric, and neonatal risk factors

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Abstract
Purpose The purpose was to explore underlying maternal, obstetric, and neonatal risk factors of retinal hemorrhages (RH) in healthy full-term newborns.
Methods A total of 1199 full-term infants, with gestational age more than 37 weeks and Apgar score of 7 or above, were included in this study. Infants with severe systemic diseases or any other eye diseases were excluded. Eye examinations with RetCamIII within 1 week of birth were performed in all infants. Maternal, obstetric, and neonatal parameters were analyzed and compared between newborns with RH and those without RH.
Results RH was seen in 294 of the 1199 infants (24.5 %) in this study. Among factors examined in the study, spontaneous vaginal delivery (SVD) (odds ratio [*OR*] =3.811 [95 % *CI*2.649–5.483], $P<0.001$) and cephalhematoma (*OR*=1.823 [95 % *CI*1.009–3.296], $P=0.047$) correlated positively with RH occurrence in newborns, while a history of cesarean delivery correlated negatively with RH occurrence (*OR*=0.296 [95 % *CI*0.139–0.630], $P=0.002$). There was no statistical correlation found between RH and the other risk factors examined in this study. These factors included gender, gestational age, birth weight, maternal age, volume, and turbidity of amniotic fluid, duration of the first or second stage of labor, anemia, hypertensive disorders complicating pregnancy (HDCP), fetal distress, intracranial hemorrhage, and neonatal hyperbilirubinemia.
Conclusions RH is common in full-term newborns. A lower prevalence of newborn RH was found in infants delivered by mothers with a history of cesarean delivery. In contrast, SVD and cephalhematoma were found to be potential risk factors for the development of newborn RH in full-term infants. Infants with these risk factors may, therefore, require greater attention in regard to RH development.

Keywords Eye examination · Retinal hemorrhage · Healthy full-term newborns · Risk factors

Introduction

During the last several decades, improvements in the diagnosis and treatment of obstetric, gynecologic, and pediatric illnesses have led to less perinatal complications in newborns. As a result of such improvements, the prevalence of newborn retinal hemorrhages (RH) has been expected to decrease. However, the reported incidence of neonatal RH remains high, though it varies widely from 2.6 to 50 %[1–3]. This variation may be due to different examination techniques, diverse patient demographics, or how soon after birth examinations are conducted [4]. During the 20th century, a direct ophthalmoscope was usually used for newborn fundus examinations. Due to the limited inspection range, newborn RH in peripheral regions was sometimes unavoidably missed. At the beginning

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of the 21st century, an indirect ophthalmoscope, which had a wider examination range for the retina, was usually employed for the primary examination of newborns. However, the inspection results were extremely subjective, as they depended strongly on the examiners' operating skills. Recently, a wide-angle fundus camera (RetCam) allowing immediate visualization and real-time recording of fundus findings has become widely used in screening of pediatric retinal diseases, including newborn RH.

Presently, the risk factors and underlying mechanisms of newborn RH still remain uncertain. To further investigate the possible risk factors of RH—including general, maternal, obstetric, and neonatal factors—we performed fundus screening on 1199 full-term newborns in the maternity department.

Methods

Subjects

Consecutive full-term infants, who had been born in the Maternity Department, Zhongshan People's Hospital, Sun Yat-San University from May to November 2012, were included in this study. Each infant had a gestational age of 37 weeks or more and an Apgar score of 7 or more. Infants with severe systemic diseases (e.g., tetralogy of fallot, phenylketonuria, etc.) or other eye diseases (e.g., congenital cataracts, primary congenital glaucoma) were excluded from the study. Infants whose mothers had known transmitted diseases were also excluded. This study was approved by the ethical committee of Zhongshan People's Hospital, Sun Yat-San University.

Collection of maternal, obstetric, and neonatal clinical data

The details of each infant's maternal, obstetric, and neonatal history were recorded. These details included maternal age (MA), values of external pelvic measurements, mode of delivery (spontaneous vaginal delivery, SVD/ Cesarean section, CS), the duration of first and second stage of labor, history of perinatal diseases such asanemia, hypertensive disorders complicating pregnancy (HDCP), history of cesarean delivery (CD), gestational diabetes mellitus (GDM), premature rupture of membranes, placental abruption, umbilical cord around fetal neck (UCAN), fetal distress, and perineal laceration. Gestational age (GA), birth weight (BW), gender, and Apgar scores of newborns were also recorded. Other neonatal factors recorded included cephalhematoma, intracranial hemorrhage, and neonatal hyperbilirubinemia.

Eye examinations

Eye examinations were performed within 1 week of birth (mean 1.907±1.25 days).All examinations, imaging capturing, and readings were performed by a medical team, which consisted of experienced retinal doctors and nurses. Firstly, the anterior segment of the eyeball and pupillary light reflex were examined using a standard flash light. Second, the pupils were dilated using 1 % tropicamide eye drops three times at 10-minute intervals. Alcaine eyedrops (Alcon Laboratories Inc., Fort Worth, TX, USA) were then applied as a topical anesthesia and a pediatric speculum was used for eyelid opening. Digital images were taken with the RetCamIII (Clarity Medical System Inc., Pleasanton, CA, USA) using a 130° lens. Two experienced reviewers (Y. Z. and.Y.Y.) read the images independently. A third senior reviewer (X.D.) was sought for resolution if the results were not consistent.

Statistical analysis

The Statistics Package for the Social Sciences (SPSS) was used to compare the maternal, obstetric, and neonatal factors between newborns with and without RH using a univariate logistic regression analysis. All variables with P values of less than 0.1 were then added to the multivariate logistic regression model to adjust for confounding factors. In the multivariate logistic model, a forward stepwise approach was performed and factors with a p value less than 0.05 were considered statistically significant.

Results

This study included 1199 healthy full-term newborns who received eye examinations. There were ten twins and 1189 single births, and the male-to-female ratio was 1.1:1. The mean GA was 39.27±1.01 weeks. The BW ranged from 2330 g to 4400 g. Among the 1199 infants, 904 infants were defined as negative and 290 infants as positive for RH in both observers, while only five infants were negative in one observer and positive in the other. The agreement of two observers was high, with a kappa score of 0.812. A third senior reviewer was sought for resolution in these five infants. RH was seen in 294 of the 1199 infants (24.5 %). In cases of RH, 184 (62.6 %) were bilateral. Macular RHs were noted in 50/294 (17.00 %) infants, and fovea-involved retinal hemorrhages were found in eight infants (2.72 %). The infants were placed into two groups: Group RH (294 infants) and Group No RH (905 infants). There were no statistical differences in gender or GA between the two groups. However, the mean MA was higher in Group RH than that of Group No RH (*OR*= 0.951 [95 % *CI* 0.922–0.981], *P*=0.002). The mean BW was

also greater in Group RH than Group No RH (*OR*=0.999 [95 % *CI* 0.999–1.000], *P*=0.009; see Table 1).

Maternal factors

Maternal factors that may contribute to RH, as suggested by previous studies [2, 5, 6], were investigated in this study. These factors included history of CD, GDM, volume, and turbidity of amniotic fluid, presence of anemia, placenta previa, and HDCP. The results of a univariate logistic analysis suggested that the full-term infants delivered by mothers with history of CD or GDM had a lower prevalence of newborn RH (*OR*= 0.148 [95 % *CI* 0.075–0.294], *P*<0.001);(*OR*=0.241 [95 % *CI* 0.051–0.905], *P*=0.036). The infants whose mother had a history of CD (161 cases) were subgrouped into SVD group (23 cases) and CS group (138 cases). RH was seen in four of the 23 infants (17.4 %) in SVD group, which was significantly higher than five of the 138 cases (3.6 %) in CS group (*P*= 0.025). No statistic significant differences were noted in the frequency of the occurrence of turbidity of amniotic fluid, presence of anemia, placenta previa, and HDCP between the two groups in our study (see Table 2).

Obstetric factors

Several obstetric clinical features examined included mode of delivery (SVD/CS/Delivery via instrument), presence of premature rupture of membranes, precipitate labor, obstetric laceration during vaginal delivery (e.g., cervical laceration, vaginal wall laceration and perineal laceration), abruption, duration of the first stage of labor, and the second stage of labor.

The prevalence of RH was higher in newborns delivered with SVD (34.01 %) and lower in those delivered via CS (9.48 %, *OR*=4.909 [95 % *CI* 3.473–6.938], *P*<0.001). Of the 23 full-term infants with precipitate labor, 11 (47.8 %) developed RH. This RH rate was much higher than the rate in infants without precipitate labor (283/1176, 24.1 %) with a significant statistical difference (*OR*=2.879 [95 % *CI* 1.256–6.596], *P*=0.012). Obstetric laceration during vaginal delivery also contributed to the prevalence of newborn RH, according to the results of a univariate logistic analysis. The other obstetric factors examined, such as postpartum hemorrhage, premature rupture of membranes, abruption, and duration of the first or second stage of labor, did not statistically correlate with the occurrence of newborn RH (Table 2).

Neonatal factors

Among the neonatal factors examined, presence of cephalhematoma (*OR* 2.313 [95 % *CI*1.331–4.020], *P*= 0.003) and UCAN (*OR*: 1.327 [95 % *CI* 1.001–1.760], *P*= 0.049) was significantly associated with the increased prevalence of RH. Other neonatal factors— including presence of fetal distress, intracranial hemorrhage, and neonatal hyperbilirubinemia—had no statistical correlation with the occurrence of newborn RH (Table 2).

Analysis of multiple logistic regression analysis

According to the results of the univariate logistic regression analysis, MA, BW, history of CD, GDM, SVD, precipitate labor, obstetric laceration during vaginal delivery, cephalhematoma, and UCAN were related to newborn RH. These factors were thus included in a multiple logistic regression analysis to adjust for confounding factors. The results showed that SVD (*OR*=3.811 [95 % *CI* 2.649–5.483], *P*<0.001), history of CD (*OR*=0.296 [95 % *CI* 0.139–0.630], *P*=0.002) and presence of cephalhematoma (*OR*= 1.823 [95 % *CI* 1.009–3.296], *P*=0.047) were significantly correlated with newborn RH in full-term infants (Table 3).

Discussion

Techniques for retinal examination have improved greatly in the last few decades. As a result, newborn RH has been found to be one of the most common neonatal abnormalities, and it is now receiving more attention by ophthalmologists and pediatricians. The prevalence of newborn RH was 34% in US studies, when screened for using Retcam [5]. In our study, the overall prevalence of healthy newborn RH was 24.5 %, which was quite close to the rates found in other Chinese studies whose newborn RH prevalence ranged from 20.2 to

Table 1 Comparison of underlying demographic factors for newborns' retinal hemorrhages in full-term infants by univariate logistic regression analysis

General factors	Newborns RH		*OR*	95.0 % *CI* for *OR*		*P*
	RH (*n*=294)	No RH (*n*=905)		Lower	Upper	
Gender	149:145	485:420	1.128	0.865	1.417	0.327
Gestation age (GA)	39.25±0.99	39.36±1.04	1.123	0.985	1.280	0.083
Maternal age (MA)	29.58±4.56	28.34±2.05	0.951	0.922	0.981	0.002[a]
Birth weight (BW)	3229±358	3166±344	0.999	0.999	1.000	0.009[a]

[a] with significant statistical difference

Table 2 Comparison of underlying obstetric factors for newborns retinal hemorrhages in full-term infants by univariate logistic regression analysis

		Newborns RH		*OR*	95.0 % *CI* for *OR*		*P*
		RH (*n*=294)	no RH (*n*=905)		Lower	Upper	
Maternal factors	History of cesarean delivery (CD)	8 (2.7 %)	153 (16.9 %)	0.137	0.067	0.283	<0.001[a]
	Gestational diabetes mellitus (GDM)	2 (0.7 %)	26 (2.9 %)	0.231	0.055	0.980	0.047[a]
	Volume of amniotic fluid (ml)	649.04±244.98	665.46±182.61	1.000	1.000	1.001	0.292
	Turbidity of amniotic fluid	22 (7.4 %)	87 (9.6 %)	0.762	0.468	1.241	0.275
	Anemia	77 (26.2 %)	32 (3.5 %)	1.040	0.750	1.443	0.813
	Placenta previa	5 (1.7 %)	30 (3.3 %)	1.034	0.596	1.792	0.906
	Hypertensive disorders complicating pregnancy (HDCP)	0 (0)	15 (1.7 %)	–	–	–	0.998
Obstetric factors	Mode of labor			4.909	3.473	6.938	<0.001[a]
	Spontaneous vaginal delivery (SVD)	250 (85.0 %)	485 (53.6 %)				
	Cesarean section (CS)	44 (15.0 %)	420 (46.4 %)				
	Precipitate labor	11 (3.7 %)	12 (1.3 %)	2.879	1.256	6.596	0.012[a]
	Cervical laceration	36 (12.2 %)	54 (6.0 %)	2.196	1.409	3.424	0.001[a]
	Vaginal wall laceration	15 (5.1 %)	22 (2.4 %)	2.155	1.103	4.212	0.025 [a]
	Perineal laceration	89 (30.3 %)	157 (17.3 %)	2.004	1.490	2.695	<0.001[a]
	Premature rupture of membranes	48 (16.3 %)	130 (14.4 %)	1.162	0.810	1.666	0.415
	Abruption	1 (0.3 %)	3 (0.3 %)	1.025	0.106	9.892	0.983
	Duration of first stage of labor (hour)	6.83±3.50	6.70±3.67	0.989	0.948	1.032	0.608
	Duration of second stage of labor (min)	37.56±28.04	35.73±26.45	0.998	0.992	1.003	0.384
Neonatal factors	Cephalhematoma	23 (7.8 %)	32 (3.5 %)	2.313	1.331	4.020	0.003 [a]
	Umbilical cord around fetal neck (UCAN)	100 (34.0 %)	255 (28.2 %)	1.327	1.001	1.760	0.049 [a]
	Fetal distress	2 (0.7 %)	9 (1.0 %)	0.681	0.146	3.170	0.625
	Intracranial hemorrhage	0 (0)	3 (0.3 %)	–	–	–	0.999
	Neonatal hyperbilirubinemia	33 (11.2 %)	72 (8.0 %)	1.461	0.946	2.257	0.087

[a] with significant statistical difference

21.5 %[6, 7], but was much lower than the prevalence rates found in Western studies [2, 5].

To date, only a few studies—all of which had small sample sizes—have focused on the risk factors of newborn RH. The results of the meta-analysis by Walts [3] showed that infants delivered by CS were less likely to develop RH, with 7.7 % of Cesarean births developing RH compared to 25.8 % infants delivered by SVD. Delivery via instrument was found to be another risk factor, as 35.5 % of births via instrument developed RH compared to the 25.6 % of SVD births without instrument that developed RH (*OR*=1.75) [3]. The present study included more potential neonatal, maternal, and obstetric risk factors than most previous studies. Our study confirmed that SVD is one of the major risk factors for newborn RH. However, in our study, only 12 infants were delivered via instrument; among those infants, 25 % (3/12) developed RH. The incidence level was close to the overall rate; however, it was not analyzed in the logistic regression model due to the small sample size.

Table 3 Multivariate analysis of significant risk factors for newborns' retinal hemorrhages in full-term infants

Risk factor	OR	95.0 % CI		*P*
		Lower	Upper	
Mode of labor	3.811	2.649	5.483	<0.001 [a]
History of cesarean delivery (CD)	0.296	0.139	0.630	0.002 [a]
Cephalhematoma	1.823	1.009	3.296	0.047 [a]

[a] With significant statistical difference

In 2007, approximately 30.5 % of pregnant women in America delivered their children via Cesarean section [8]. Similarly, the CS rate in Europe was 22 % in 2008 [9]. However, the overall rate of CS in southeast China increased from 22 % in 1994 to 56 % in 2006 [10]. In 2001, Emerson examined 149 healthy newborns born in the US and found that while the prevalence of newborn RH in this sample was 34 %, the rate of CS was only 11.11 % [2]. In the UK in 2006, Hughes found that the prevalence of newborn RH was 34 % in 53 newborns, while the CS rate in this group was 32 % {Hughes, 2006 #185}. However, in our present study, a higher CS rate was noted (38.7 %), while there was a lower prevalence of newborn RH (24.5 %). Therefore, we suggest

that the higher Cesarean section rate is at least one possible factor contributing to the relatively low incidence of newborn RH in China. On the other hand, a history of CD has been suggested as a protective factor of newborn RH in this study (*OR* 0.296 [95 % *CI* 0.139–0.630], *P*=0.002). However, the history of CD is one of the operative indications of Cesarean section, most mothers with a history of CD had Cesarean sections. Therefore, we suggested that the history of CD might be an indirect factor for the occurrence of newborn RH.

We found that cephalhematoma may be a risk factor for newborn RH (*OR*=1.823 [95 % *CI* 1.009–3.296], *P*=0.047). The possible causes of cephalhematoma include fetal head compression in the bony birth canal, birth via instrument, abnormal clotting functions, and imperfect vessel walls in neonates, which may increase intracranial pressure and subsequently lead to cephalic venous congestion. RH is believed to be caused by the rupture of superficial retinal capillaries as a result of increased venous pressure. Therefore, fetal head compression was suggested as the underlying mechanism of newborn RH.

In our study, GDM was shown as a protective factor using a single logistic analysis instead of a multiple logistic analysis, making this finding difficult to expand upon, especially because of the low incidence of diabetes reported in our study (28/1199). More studies using larger samples of pregnant women with GDM are required to confirm our results and to reveal the underlying mechanisms. Some studies focused on newborn RH reported that HDCP, fetal distress and higher maternal age were risk factors for newborn RH [2, 6]. However, there were only 15 cases of HDCP and three cases of intracranial hemorrhage in our study. No RH was found in the infants whose mothers experienced HDCP, and only two of the 11 cases of fetal distress had newborn RH. These negative findings are difficult to interpret, as the number of subjects is not big enough to reach any statistically relevant conclusions. Similarly, precipitate labor, obstetric laceration, and UCAN have a correlation with the prevalence of RH in newborns by using univariate logistic analysis, while they have no correlation by using multiple logistic analysis. These contradictory results may be explained by these factors playing a role in newborn RH by affecting the mode of labor.

This study is limited by its single-center origin and lack of community epidemiologic data. Because Zhongshan People's Hospital is the largest urban medical center in southern China, and because it has advanced obstetric, gynecologic, and pediatric diagnosis and treatment capabilities, less perinatal complications were found during pregnancy and delivery than may be found in other hospitals. The sample of full-term newborns in our study is, therefore, not representative of the population.

Overall, RH is one of the most common ocular abnormities in newborn infants. The mode of delivery and the presence of cephalhematoma may be risk factors for newborn RH in full-term infants. Infants with such risk factors require much more observation. Understanding the possible risk factors and the underlying mechanisms of RH, especially moderate to severe RH, can help develop the long-term understanding of visual function abnormalities like oblique amblyopia and refractive errors. Further studies on the natural outcomes of RH will continue to shed light on visual impairment in children.

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The various contributors and their contributions were: design and conduct of study (Q.Z., Y.Z., X.D.); collection of data (Y.Z., Y.Y., Z.L., Y.L., C.W.); management, analysis, and interpretation of data (Y.Y., R.L.); preparation of the manuscript (X.D., Y.Y.); and review and approval of manuscript (X.D., Y.Y.).

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