Chronic Peripheral Separation of Placenta

The Significance of Diffuse Chorioamnionic Hemosiderosis

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Key Words: Abruptio placentae; Chronic abruption; Circumvallate; Hemosiderin; Peripheral separation; Placenta; Prematurity

Abstract

Diffuse nonmeconium-related pigment was observed in the chorioamnion of 36 of 1,023 placentas over 4 years and evaluated by iron staining. Stains were negative in 13 cases and positive in chorionic plate and membranes (diffuse chorioamnionic hemosiderosis [DCH]) in 23 cases (3/1,000 deliveries; 25/1,000 placentas). Gestational age at delivery was lower in DCH and was inversely proportional to the magnitude of iron staining. Placentas with DCH were more likely to show circumvallation, old peripheral blood clots, increased chorionic-villous macrophages, and green discoloration. To evaluate demographic, obstetric, and perinatal factors associated with DCH, 2 gestational age–matched controls were selected for each DCH case. Multiparity, smoking, and chronic vaginal bleeding all were increased significantly with DCH, while intrauterine growth retardation and oligohydramnios were increased but did not achieve statistical significance. Gestational hypertension and advanced maternal age were significantly decreased with DCH, and cocaine abuse was uncommon (3 cases). Long-term neurologic sequelae of DCH were evaluated in a separate series of gestational age–matched very-low-birth-weight infants with and without neurologic impairment at 2 years of age. No increased risk of neurologic impairment was found in patients with DCH.

Chronic peripheral separation of the placenta from the uterine implantation site, also known as the chronic abruption-oligohydramnios sequence (CAOS), is characterized clinically by recurrent episodes of substantial vaginal bleeding beginning in the early second trimester of pregnancy.[1,2] In some patients, such bleeding may be associated with periplacental hemorrhages of sufficient extent to be detected by antenatal ultrasonography, but in the absence of a positive ultrasonographic result, assessment of the significance of a history of vaginal bleeding often can be difficult.[3–5] Pathologic findings suggestive of chronic peripheral separation include old and recent peripheral blood clots and circumvallate membrane insertion.[6] Many of these findings are observer-dependent, difficult to quantitate, and relatively nonspecific, showing overlap with other processes, such as abruptio placentae, placenta previa, and circummarginate membrane insertion.

Substantial amounts of retroplacental hemorrhage associated with chronic peripheral separation result in the release of blood and blood breakdown products into the amniotic fluid. As in meconium exposure, this exogenous material is phagocytosed by chorionic macrophages. The resulting hemoglobin breakdown products are deposited as hemosiderin crystals, which can be quantified by histochemical staining techniques for iron. This process of macrophage response, RBC uptake, and metabolism to hemosiderin has been estimated to take 3 to 8 days in other tissues.[7,8] In the present study, we used histochemically confirmed diffuse chorioamnionic hemosiderosis (DCH) as an objective and relatively observer-independent indicator of chronic peripheral separation, which can be evaluated in sections of chorionic plate, membranes, or both. Relationships between DCH and other placental lesions were explored by using a placental database. Obstetric correlates were determined in a case-control study using data from linked placental and obstetric databases. Possible long-term neurologic impairment at 2 years of age in patients with

DCH was evaluated in a case-control study using data from a separate neonatal database.

Materials and Methods

During a 4-year period between July 1, 1991, and July 1, 1995, clinical and pathologic data from 1,023 singleton placentas examined by one us (R.W.R.) were entered into a placental pathology database. The overall rate of placental submission during this period was 12.6%. Criteria for submission were as specified in guidelines of the College of American Pathologists and included all patients with a history of antenatal hemorrhage or preterm birth at less than 37 weeks' gestation.[9] Patients with a clinical history of placenta previa were excluded. All placentas were examined and processed using a standard protocol in the pediatric pathology section at University Hospitals of Cleveland, Cleveland, OH.[10] Chorioamnionic pigment was evaluated by using light microscopy in membranes and chorionic plate. Cases with a clinical history of meconium-stained fluid and the appropriate pathologic findings of membrane degenerative change and dusty brown pigment within vacuolated macrophages were classified as "features suggestive of meconium" and not further studied.[11] Sections of chorionic plate and membrane roll from all other cases with diffuse chorioamnionic pigment were stained for iron by using the Gomori method.[12] Placentas negative by iron stain were not further evaluated to determine the nature of the pigment.

Criteria for placental diagnoses were as specified by a recent consensus report of the College of American Pathologists.[9] Venous hemorrhages arose in distended veins at the periphery of the placental disk. Veins were identified by their oblique course, luminal distention, and a lack of either physiologic conversion or a thick muscularized wall. *Circumvallation* was defined as insertion of the membranes 1 cm or more inside the perimeter of the placental disk with a histologically confirmed peri-insertional rim of fibrin or old blood clot. At least 33% of the total circumference had to be affected. *Old peripheral blood clot* was defined as the presence of adherent pale red-brown blood clot at least 0.5 cm in maximum diameter and contiguous with the perimeter of the placental disk.

Demographic, obstetric, and perinatal factors associated with DCH were evaluated in a case-control analysis in which each of the 23 cases with DCH was matched with the next 2 placentas in the database of the same gestational age lacking DCH. Clinical data were obtained from a database of all deliveries maintained in the Department of Obstetrics and Gynecology. *Gestational hypertension* was defined as preeclampsia or a history of chronic hypertension with diastolic pressure greater than 90 mm Hg during gestation. *Second-trimester bleeding* was defined by any discrete episode of vaginal bleeding reported to the clinician between 13 and 26 weeks' gestation. *Prolonged rupture of membranes* was defined as clinically confirmed rupture of membranes 24 or more hours before delivery. *Monitoring abnormalities* were defined as late decelerations or variable decelerations with a late component. *Intrauterine growth retardation* was defined as birth weight less than the 10th percentile expected for gestational age. *Oligohydramnios* was defined as a maximum amniotic fluid pocket less than 1 cm by ultrasonography.

Long-term neurologic outcome was evaluated in a separate population of inborn singleton very-low-birth-weight infants admitted to the neonatal intensive care unit at University Hospitals of Cleveland between the years of 1983 and 1991 and followed up in a high-risk follow-up program.[13] The patients evaluated in this report were a subset of those analyzed in a recent retrospective case-control study of clinical factors determining neurologic impairment in very-low-birth-weight infants. Details of case selection and the criteria for neurologic impairment are described elsewhere.[14] In that study, 72 infants were diagnosed with major neurologic impairment at 20 months corrected age. Each case was matched by weight (±250 g), gestational age (±2 weeks), race, and sex to a control infant born during the same year and having normal neurologic examination results at 20 months. Placental reports and slides were available in 119 of the 144 original study patients (60 cases and 59 controls). Placentas were not submitted to pathology for the remaining cases. Among patients with placentas available for study, gestational age, race, and sex were equivalent (data not shown). All placentas were examined and processed using the same protocol described in the preceding text. Slides and reports were reviewed in a blinded fashion. Diagnoses were entered into a database using a hierarchical classification scheme by 1 pathologist (R.W.R.). Criteria for DCH were the same as those specified above.

Statistical Analysis

The χ^2 analysis or Fisher exact tests were used for discrete data. Significance for differences in nonpaired analyses using the placental database was expressed using *P* values. Results of case-control analyses were expressed as odds ratios and 95% confidence intervals.

Results

Prevalence of Chorioamnionic Pigment

Diffuse pigment deposition was found in the chorioamnionic layers of the chorionic plate and/or membranes of 206

of 1,023 placentas examined ▮Table 1▮. Features consistent with meconium exposure, including dusty or globular red-brown coloration, prominent cytoplasmic vacuolation of macrophages, and a clinical history of meconium-stained amniotic fluid, were found in 170 cases. Sections of the chorionic plate and membranes in the remaining 36 cases were stained for iron by using the Gomori method. Iron positivity was found in 23 cases (2.5% of placentas submitted) ▮Image 1A▮. These cases all had golden brown refractile hemosiderin granules extracellularly or within macrophages ▮Image 1B▮. In our experience, hemosiderin rarely is found in placentas examined for various reasons without specific indications for submission (unpublished data). Assuming that this is true, the overall incidence of DCH would be approximately 3 per 1,000 live-born singleton deliveries during the period of the study. The remaining 13 cases without stainable iron were similar to the positive cases in mean gestational age (32.8 weeks) and associated pathologic changes (77% with circumvallation and 31% with old peripheral blood clot). As discussed in the following text, some of these placentas may represent cases of chronic peripheral separation in which hemoglobin degradation products lack accessible ferric iron. Other possible origins for pigment in these cases include atypical meconium or lipofuscin.

Other Pathologic Features Associated With DCH

Circumvallation was seen commonly and was significantly associated with DCH (57% in cases *vs* 2.5% in controls, $P < .001$) ▮Table 2▮. Most circumvallate placentas without DCH (18/25 cases) had iron-stain–negative chorioamnionic pigments not suggestive of meconium exposure. Old peripheral blood clots derived from peripheral venous hemorrhage ▮Image 1C▮ and ▮Image 1D▮ also were increased significantly with DCH (44% in cases *vs* 6.5% in controls, $P < .001$). Other characteristic features found in placentas with DCH included diffusely increased stromal macrophages in the chorionic plate and villi, recent peripheral blood clots, nonspecific decidual lymphocytic infiltrates, and green discoloration of the chorionic plate. Green discoloration has been attributed to hemoglobin breakdown products, such as biliverdin, and was seen in 12 of 23 cases of DCH. Green color also was found in 2 of the 13 iron-negative cases lacking typical features of meconium exposure.

▮Table 1▮
Prevalence of Chorioamnionic Pigment in 1,023 Consecutively Examined Placentas

	No. (%)
Total no. with pigment	206 (20.14)
Features suggestive of meconium*	170 (16.62)
Nonmeconium pigment	36 (3.52)
Iron-stain negative	13 (1.27)
Iron-stain positive	23 (2.25)

* Dusty brown pigment within vacuolated macrophages of patients with a positive clinical history of meconium-stained fluid (supported by acute amniotic degeneration and edema in most cases).

▮Table 2▮
Pathologic Features Associated With Chorioamnionic Hemosiderosis

	Hemosiderin-Positive* (n = 23)	Hemosiderin-Negative (n = 1,000)
Circumvallation	13†	25
Old peripheral blood clot	10†	65

* Other pathologic features seen in hemosiderin-positive cases: increased macrophages-chorionic plate, 18; peripheral decidual necrosis, 17; green discoloration of fetal surface, 12; increased macrophages-villous stroma, 11; recent peripheral blood clot, 7.
† $P < .001$.

Clinical Features of DCH

The most common pregnancy complication associated with DCH was prematurity ▮Table 3▮. Delivery at less than 37 weeks' gestation was seen in 83% of DCH cases *vs* 44.3% of non-DCH cases ($P < .001$). Furthermore, the magnitude of iron positivity, assessed semiquantitatively from stained sections, was inversely proportional to the mean gestational age. Mean gestational ages for mild, moderate, and severe DCH were 34.7, 33.5, and 28.8 weeks, respectively. Other antenatal and perinatal features of DCH were evaluated in a case-control analysis in which each DCH case was matched with the next 2 non-DCH cases of the same gestational age in the database ▮Table 4▮. Clinical information was abstracted in a blinded fashion from a departmental obstetric database. Patients with DCH were more likely to be multigravid and smoke cigarettes but less likely to older than 34 years or have gestational hypertension. As expected, a history of first- and second-trimester vaginal bleeding was strongly associated with DCH. Two other factors, intrauterine growth retardation and oligohydramnios, also were increased with DCH, but statistical significance was not achieved. Prolonged rupture of membranes also was increased to a nonsignificant degree (30% in cases *vs* 20% in controls). A history of cocaine abuse was uncommon in both groups (3 cases and 1 control).

Relationship Between DCH and Neurologic Impairment in Very-Low-Birth-Weight Infants

Neurodevelopmental abnormalities and DCH are both increased among very-low-birth-weight infants.[15,16] To test the hypothesis that chronic peripheral separation as indicated by DCH may contribute to neurologic impairment, we used data from a separate cohort of infants born, treated, and followed up at our institution between 1983 and 1991. Details of this population are listed in the "Materials and Methods" section and in previous articles.[13,14] DCH was

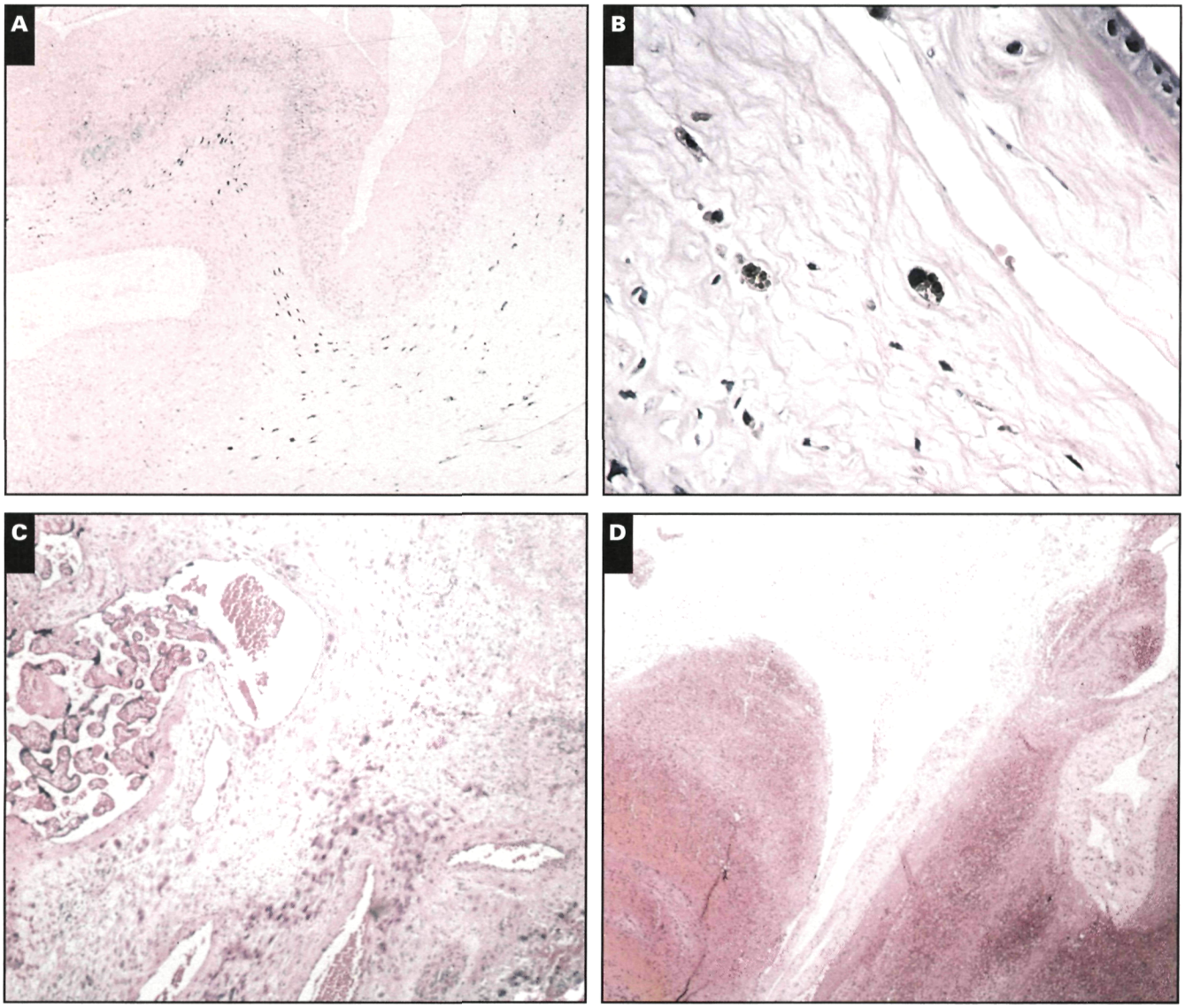

Image 1 Pathologic features of chronic peripheral separation with chorioamnionic hemosiderosis. A, Membrane roll showing diffuse blue iron staining of crystalline pigment in the amnion and chorion (Gomori iron, ×250). B, Peripheral chorionic plate showing refractile golden brown hemosiderin crystals (H&E, ×400). C, Distended and hyperangulated peripheral veins in direct contiguity to the lateral intervillous space (H&E, ×250). D, Recent peripheral venous hemorrhage involving veins in the same location as those illustrated in C (H&E, ×250).

found in 13% of neurologically impaired infants compared with 15% of controls, and there was no evidence of a dose-response effect between intensity of DCH and neurologic impairment **Table 5**.

Discussion

Antenatal vaginal bleeding is an important risk factor for adverse maternal and fetal outcome.[17,18] Separating the most serious cause of vaginal bleeding, abruptio placentae, from other causes, such as marginal abruption, terminal abruption, and chronic abruption, can be a difficult clinical distinction. Pathologic examination often does little to clarify the situation. In 1 large study attempting to correlate pathologic retroplacental hemorrhages with the clinical diagnosis of abruptio placentae, the 2 diagnoses were found to agree in only about one third of cases, with the remaining diagnoses split evenly between pathologic hemorrhages without clinical symptomatology and clinical abruptions without pathologic retroplacental hemorrhages.[19] Ultrasonographers have separated hemorrhages associated with vaginal bleeding into 3 categories; retroplacental (between placenta and uterus), preplacental (at the disk margin), and subchorionic

Table 3
Gestational Age at Delivery Is Decreased in Chorioamnionic Hemosiderosis and Is Inversely Related to the Magnitude of Iron Positivity

	N	Gestational Age	
		< 37 Weeks	Mean
Hemosiderin-positive			
Mild	3	2	34.7
Moderate	14	11	33.5
Severe	6	6	28.8
Total	23	19*	32.4
Hemosiderin-negative	1,000	443	35.7

*$P < .001$, increased proportion <37 weeks in hemosiderin-positive *vs* hemosiderin-negative.

Table 5
Prevalence of Chorioamnionic Hemosiderin in 60 Very-Low-Birth-Weight Infants With Neurologic Impairment at 2 Years of Age and 59 Matched Control Subjects

	Neurologic Impairment (n = 60)	Control Subjects (n = 59)
Chorioamnionic hemosiderin		
Mild	3	2
Moderate	2	6
Severe	3	1
Total no. (%)	8 (13)*	9 (15)

* Odds ratio, 0.86; 95% confidence interval, 0.31–2.39; chorioamnionic hemosiderin with neurologic impairment *vs* control.

(between membranes and uterus). In this scheme, central retroplacental hemorrhages were found to have a later onset and a worse prognosis than the other 2 entities, which usually began at the margin of the placenta during the first half of pregnancy.[3]

Although not proved, 1 hypothesis that helps to explain some of the ambiguities is that retroplacental hemorrhages fall into 2 broad categories: arterial and venous.[20] In this scenario, arterial bleeding leads to abruptio placentae, while marginal, terminal, and chronic abruptions represent venous hemorrhage. Arterial blood flow is maximal in the central two thirds of the placenta, and arterial pressure exceeds venous pressure. Therefore, abruptio placentae is more likely to be centrally located, to be destructive with indentation and rupture of the basal plate, and to result in rapid delivery often accompanied by fetal hypoxia.[21] Factors predisposing to arterial hemorrhage include underlying arterial wall disease as seen in preeclampsia,[22,23] ischemia-reperfusion injury as seen with cocaine abuse,[24] and shear stress secondary to traumatic injuries, such as falls or motor vehicle crashes.[25] Venous hemorrhages, on the other hand, tend to be peripheral, arising from chronically distended veins. These peripheral veins, which were at one time referred to as the *marginal sinus*,[20] are less well supported than central veins. In part, this is due to less extracellular matrix, which preferentially accumulates around central arteries that have undergone physiologic change. Two additional factors contributing to increased fragility of peripheral veins are increased volume secondary to lateral displacement of old blood as fresh arterial blood enters the central portion of the intervillous space and acute angulation acquired as a consequence of lateral placental growth.[26] Since venous pressure

Table 4
Gestational Age–Matched Case-Control Analysis of Antenatal and Birth Characteristics of Mothers and Infants With Chorioamnionic Hemosiderosis

	Percentage Positive		
	Cases (n = 23)	Controls (n = 46)	Odds Ratio (95% Confidence Interval)
Age (y)			
<20	13	13	1.00 (0.23–4.42)
>34	0	15	0.85* (0.75–0.96)
Primigravida	13	50	0.15* (0.04–0.68)
Previous miscarriage†	40	35	1.25 (0.36–4.32)
Previous premature delivery†	15	22	0.64 (0.13–3.08)
Smoking	43	20	3.16* (1.05–9.50)
Gestational hypertension	0	20	0.81* (0.70–0.93)
Second-trimester bleeding	61	11	12.76* (3.65–44.5)
Oligohydramnios	26	9	3.71 (0.93–14.8)
Rupture of membranes, >24 h	30	20	1.80 (0.57–5.67)
Monitoring abnormalities	22	44	0.36 (0.11–1.14)
Intrauterine growth retardation (<10th percentile)	26	9	3.71 (0.93–14.8)
Apgar score <6			
At 1 min	30	41	0.62 (0.21–1.80)
At 5 min	22	17	1.32 (0.38–4.61)

* $P < .05$.
† Percentage of multigravid patients.

is less than arterial pressure, venous hemorrhages are less destructive and do not necessarily lead to immediate delivery. Three factors thought to contribute to peripheral venous hemorrhage are increased central venous pressure,[26,27] abnormal placentation with poor lateral structural support,[28] and changes in uterine shape as may occur with premature lower uterine-cervical relaxation or premature rupture of membranes.[26,29]

Based on the features described in the present report, DCH seems to be the pathologic correlate of the recently described CAOS. CAOS manifests with substantial blood loss beginning at around 19 weeks' gestation. Amniotic fluid volume is normal initially but gradually progresses to oligohydramnios. CAOS typically results in premature delivery at 28 ± 5 weeks' gestation.[1] Sonographic findings in CAOS may include preplacental (peripheral) and subchorionic (retromembranous) collections of blood.[3–5] Many cases of CAOS have premature rupture of membranes, although in some cases, membrane rupture is simulated by organization of peripheral blood clots with clot retraction and subsequent passage of serum through the vagina.[2]

Placental circumvallation was the most common pathologic feature associated with DCH. The pathogenesis of circumvallation is believed by most to be peripheral venous hemorrhage with extension of blood upward and inward along the chorionic plate.[2,30] Such hemorrhage results in displacement of the membrane insertion site away from the margin of the disk. Whether all circumvallate placentas originate in this manner remains controversial, but the present study demonstrates once again the strong relationship between circumvallation and other features of chronic peripheral separation. The alternative hypothesis that circumvallation represents a developmental anomaly predisposing to, rather than resulting from, peripheral venous hemorrhage[28] is contradicted by a case report of ultrasonographic demonstration of the gradual development of circumvallation in an initially normal placenta after multiple episodes of peripheral (preplacental) hemorrhage.[31]

Clinically useful placental diagnoses should be objective, quantifiable, and independent of sampling bias. Unfortunately, many features of chronic peripheral separation, such as circumvallation and old peripheral blood clots, are subjective, nonspecific, and of uncertain pathogenesis. DCH fulfills criteria for a useful diagnosis and, as shown in the present study, correlates well with clinical and other pathologic aspects of chronic peripheral separation. DCH results from the clearance of maternal RBCs that leak into the amniotic fluid with retroplacental hemorrhage.[2] Breakdown to hemosiderin requires and parallels the degree of local macrophage infiltration and has been shown to take 3 to 8 days in other organ systems.[7,8] Hemoglobin from RBCs is cleaved by the macrophage to globin protein and heme.[32] Heme is further catabolized to the green protoporphyrin metabolite, biliverdin, and to ferric iron, which is loosely associated with surrounding proteins to form refractile iron-oxide (hemosiderin) crystals. Demonstration of iron in these crystals depends on its loose association with surrounding proteins.[33] Some cases of otherwise typical chronic peripheral separation with nonstainable chorioamnionic pigment, particularly those associated with green biliverdin staining, may be explained by inaccessibility to the iron stain.

Risk factors for DCH (CAOS) identified in the present study and in previous reports include multiparity and maternal smoking.[34,35] In contrast with abruptio placentae, gestational hypertension was significantly decreased in our population.[36,37] Placentas with DCH also were more likely to be associated with second-trimester bleeding, prolonged rupture of membranes, oligohydramnios, and intrauterine growth retardation. Most of these latter complications have been observed in at least 1 previous report.[1,2,29,34]

Several factors have been related to an increased risk for neurologic injury in very-low-birth-weight infants, including chorioamnionitis, chorionic vessel thrombi, and diffuse villous edema.[38,39] The relationship between antenatal hemorrhage and neurologic impairment has been controversial, in part owing to the difficulties in separating DCH (CAOS) from abruptio placentae.[40,41,42] While the number of cases in the present study was low, there was no indication of a relationship between DCH and neurologic impairment, even in the most severe subgroup. While larger prospective studies are required to confirm this result, it is possible that previous suggestions that DCH (CAOS) is associated with neurologic impairment could be due to inclusion of cases of abruptio placentae or CAOS (DCH) with superimposed abruptio placentae.[40]

In conclusion, DCH is an objective, readily quantifiable indicator of chronic peripheral separation and clinical CAOS. It is strongly correlated with other pathologic findings, such as circumvallation, old peripheral blood clots, increased chorionic-villous macrophages, and green discoloration. A smaller group of patients have similar characteristics but lack stainable iron. The correct classification of these patients is problematic and should be dealt with on an individual basis. The most important clinical consequences of this lesion are premature delivery at a gestational age inversely proportional to the magnitude of DCH and an increased risk of intrauterine growth retardation.

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