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Khong, T. Y.; Toering, T. J.; Erwich, Jan Jaap H. M.

Published in:
Pathology

DOI:
10.3109/00313020903494094

Publication date:
2010

Pathology (February 2010) **42(2)**, pp. 119–124

ANATOMICAL PATHOLOGY

Haemosiderosis in the placenta does not appear to be related to chronic placental separation or adverse neonatal outcome

T. Y. KHONG*, T. J. TOERING*† AND J. J. H. M. ERWICH†

*SA Pathology, Women's and Children's Hospital, Adelaide, South Australia; †Department of Obstetrics, University Medical Centre Groningen, Groningen, The Netherlands

Summary

Aims: To ascertain the incidence and to review the obstetric and neonatal correlates of placental haemosiderosis. Secondly, to determine if placental haemosiderosis is due to blood contamination during placental handling.

Methods: One hundred consecutive singleton placentas with and 113 consecutive singleton placentas from uncomplicated pregnancies without an indication for pathological examination were stained for iron to detect haemosiderosis in the membranes, chorionic plate and/or basal plate. The obstetric and neonatal data were analysed. In the second part, maternal retroplacental blood was placed on the chorionic plates of 15 placentas for 1, 3, 4 and 5 days prior to sampling and examination for iron deposition.

Results: Haemosiderosis was observed in 110 of 213 (51.6%) placentas. Early decelerations during fetal heart rate monitoring ($p = 0.0498$) and, negatively, maternal thrombophilia ($p = 0.0496$) were related to haemosiderosis in the placenta. Preterm delivery, chronic separation of the placenta or procedures performed during pregnancy or delivery were not significantly related to haemosiderosis. Different patterns of iron staining were observed but these were not correlated with any maternal or neonatal factors. In the experimental study, haemosiderin was not found in sections taken at various time intervals from both blood contaminated and blood contamination-free parts of the placentas.

Conclusions: Haemosiderosis in the placenta is not an artefact of placental handling. Haemosiderosis is seen considerably more frequently than previously reported and may be physiological. Haemosiderosis is not a useful indicator for chronic placental abruption and adverse neonatal outcome is not significantly correlated with placental haemosiderosis.

Key words: Placenta, haemosiderin, chronic abruption, neonatal outcome.

Received 13 July, revised 27 August, accepted 28 August 2009

INTRODUCTION

Iron pigment staining in the membranes and in the chorionic plate of the placenta, defined as diffuse chorioamnionic haemosiderosis (DCH), has been described as an objective marker of chronic placental separation. Redline and Wilson-Costello found that placentas with DCH were more likely to show circumvallation, old peripheral blood clots, increased chorionic-villous macrophages, and green discolouration. Multiparity, smoking, and chronic vaginal bleeding were all significantly associated with DCH, while the incidence of intrauterine growth restriction and oligohydramnios were increased but did not achieve statistical significance.[1] Another study found that placentas with DCH were more likely to show old peripheral blood clots, marginal haematoma and circumvallation. Amniotic necrosis was significantly more frequent in the DCH group and the incidence of recurrent episodes of vaginal bleeding, oligohydramnios and chronic abruption syndrome were significantly higher in the DCH group. This study also found that DCH was closely associated with preterm delivery, pulmonary hypertension of the newborn and dry lung syndrome and was a significant risk factor for chronic lung disease.[2]

The purpose of our study was to reassess the obstetric and neonatal correlates of haemosiderin-laden macrophages in the chorionic and/or basal plate of the placenta and membranes. Secondly, we wished to investigate whether iron deposition in the chorionic plate and membranes can be due to an artefact of placental handling. The rationale for the second part of the study was predicated by the anatomy of the placenta in relation to its separation. The presence of haemosiderin-laden macrophages diffusely distributed through the amniochorial membranes and chorionic plate, i.e., the fetal side of the placenta, is counter-intuitive to retroplacental haemorrhage occurring on the maternal side of the placenta where focal haemosiderin-laden macrophages would be expected to be seen in the placental basal plate in the area of accumulated blood at the site of placental separation from the uterus.

MATERIALS AND METHODS

Case review

Two groups of placentas were used for this study. The first group, the pathological examination-indicated, comprised 100 consecutive singleton placentas submitted for pathological examination because of one or more indications according to the College of American Pathologists' guidelines[3] over a 2-month period from December 2006 to January 2007. The second group, the non-pathological examination-indicated, comprised 113 singleton placentas that did not have indications for pathological examination from placentas consecutively collected from all pregnancies during June 1998. Collection and processing of placentas were similar over the two time periods. All placentas were processed using a standard protocol. A full thickness cross-section of the placenta and a section of the amniochorial membranes were cut at 4 μm and stained for haemosiderin with the Perls' Prussian Blue technique.

All sections were evaluated for the presence of haemosiderin using light microscopy blinded to clinical data (by two authors, TJT and TYK).

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: 10.3109/00313020903494094

Where present, the site of haemosiderin deposition was noted for each case: chorionic plate, basal plate or membranes; the last was further qualified to the amniotic, chorionic layer or decidual layer, or in a combination of the layers. Haemosiderin deposition in the membrane roll sections were graded as mild, moderate or severe, based on the extent and the density of the haemosiderin deposition. The extent of the haemosiderosis was classified as diffuse when haemosiderin deposition existed in five or more adjacent high power fields (HPF; $\times 20$ objective lens), or as localised when haemosiderin occurred in fewer than five adjacent HPF. The density of the haemosiderosis was defined as high when there were 10 or more haemosiderin-laden macrophages in one HPF ($\times 20$ objective lens), or as low when there were fewer than 10 haemosiderin-laden macrophages. Membrane roll sections with a localised and low density haemosiderosis were graded as mild haemosiderosis; sections with a diffuse and high density haemosiderosis were graded as severe haemosiderosis; the rest of the haemosiderin-positive membrane-sections were graded as moderate haemosiderosis. This grading was done for each layer of the membranes by two authors (TJT, TYK) and differences in grading were resolved by double-headed microscopy review.

Obstetric complications, procedures done during pregnancy or delivery and clinical factors of mother and fetus, which might correlate with placental haemosiderosis, were reviewed from the hospital Clinical Information Services database containing pregnancy and outcome details of every live birth and late fetal death delivered in the hospital. The following clinical data were analysed.

Obstetric complications in current or previous pregnancy were: polyhydramnios, defined as >8 cm of the largest vertical amniotic fluid pocket by ultrasonography or above 25 cm of amniotic fluid index (AFI); oligohydramnios, defined as <2 cm of the largest vertical amniotic fluid pocket by ultrasonography or below 5 cm of AFI; preterm prelabour rupture of membranes (PPROM), defined as clinically confirmed rupture of membranes before the onset of uterine contractions at a gestational age below 37 weeks; premature labour, defined as labour before 37 completed weeks of gestation; abruption of the placenta, defined as clinically confirmed premature separation of a normally implanted placenta prior to delivery; chorioamnionitis, defined as the presence of maternal fever of greater than 38°C and at least two of the following conditions: maternal leukocytosis ($>15\,000$ cells mm^{-3}), maternal tachycardia (>100 beats/min), fetal tachycardia (>160 beats/min), uterine tenderness, foul odour of the amniotic fluid; placenta praevia, defined as the presence of placental tissue overlying or proximate to the internal cervical os by ultrasonography; gestational hypertension, defined as a systolic blood pressure $\geq$l40 mmHg or diastolic blood pressure $\geq$90 mmHg in a woman who was normotensive prior to 20 weeks of gestation; pre-eclampsia, defined as pre-existing hypertension with new onset of proteinuria ($\geq$0.3 g protein in a 24 h urine specimen) after 20 weeks of gestation and an exacerbation of blood pressure to the severe range (systolic $\geq$l60 mmHg or diastolic $\geq$110 mmHg) in the last half of pregnancy; intrauterine growth restriction (IUGR), defined as birth weight $<$10th percentile expected for gestational age; elective and/or emergent caesarean section.

Procedures done during pregnancy or delivery, which might lead to intra-amniotic bleeding were: umbilical cord blood sampling; intrauterine fetal transfusion; amniocentesis; chorionic villous sampling; fetal scalp blood monitoring.

Clinical factors of the mother were: tobacco use during pregnancy; tobacco use before pregnancy, but not during pregnancy; age <20 years and >34 years; gravida ($G > 0$); grand multiparity ($P > 5$); maternal thrombophilia; previous stillbirth.

Clinical factors of the baby were: sex; fetal distress; fetal monitoring abnormalities including: early deceleration, late deceleration, variable deceleration, reduced variability, bradycardia and tachycardia; meconium stained liquor (MSL); low Apgar score at 1 min and 5 min (0–3 was defined as critically low, 4–7 was defined as fairly low); admission into neonatal intensive care unit (NICU); congenital abnormalities in general and gastrointestinal tract abnormalities in particular.[4]

Statistical analysis

The data of the two groups, haemosiderin positive cases and haemosiderin negative cases, were analysed for differences using the χ^2 analysis or Fisher exact tests. A p value ≤ 0.05 was considered statistically significant.

Experimental study

Fifteen singleton term placentas, with intact membranes, from uncomplicated pregnancies were randomly collected and processed within 30 min after delivery. Upon receipt of the placenta from the delivery room (day 0) a cross-section of the chorionic plate was taken and fixed immediately in formalin, processed routinely and subsequently stained with Perls' stain. The placenta was subsequently included in the experiment when no haemosiderin was found in this cross-section of the chorionic plate.

After taking the test section, the placenta was divided into two parts. One half of the placenta was rinsed briefly with water to ensure that the chorionic plate was not in contact with fetal or maternal blood. To simulate contamination of the fetal surface of the placenta by blood spilling from an avulsed or cut end of the umbilical cord or from maternal blood, blood obtained from the umbilical cord was placed on the surface of the chorionic plate of the other half of the placenta. Both halves of placentas were placed in separate closed buckets at room temperature (21°C) for the first 24 h as macrophages are less active at lower temperatures.[5] After 24 hours (day 1) another cross-section of the chorionic plate was taken from each half of the placenta (with blood contact and without blood contact). These sections were also fixed in formalin, processed as described above and stained for haemosiderin with Perls' staining. To simulate any potential delay in delivery-to-fixation of the placenta, and in accordance with the normal work routine, the two halves of the placenta were then placed in separate closed buckets at 4°C to prevent autolysis of the placenta: five placentas were kept in the fridge for 48 h (until day 3), five for 72 h (until day 4) and the remaining five for 96 h (until day 5), at which point the last cross-section of the chorionic plate was taken from the two halves of the placenta. These sections were fixed in formalin, processed as described above and stained for haemosiderin with Perls' staining and sections of the placentas were evaluated for haemosiderosis in the chorionic plate using the same criteria as those specified above.

RESULTS

Case review

Iron stain positive pigment deposition (haemosiderosis) was found in 110 of the 213 placentas examined (51.6% of all placentas). The incidence was 49.0% in the pathological examination-indicated group (49/100) and 54.0% in the non-pathological examination-indicated group (61/113). Haemosiderosis was seen in the membranes and/or chorionic plate and/or basal plate in various combinations (detailed data available from authors).

Haemosiderosis was seen most frequently (103/110; 93.6%) in the extraplacental membranes. Within this group of 103 haemosiderin-positive membranes, it was most frequently seen in the chorionic layer (89/103); it was seen only in the chorionic layer of the membranes and not other locations simultaneously in 41 cases and in combination with haemosiderosis in the chorionic and/or basal plates in 10 cases. In 35 cases (34.0%) haemosiderosis was found in the chorionic and decidual layers but not in the amniotic layer.

Haemosiderin was seen in the chorionic plate in 18 cases (16.4%); in only five cases was haemosiderosis present in the chorionic plate but not at other locations. Haemosiderin was seen in the basal plate of the placenta in 18 cases (16.4%); in one case it was seen only in the basal plate but not at other locations. In one case it was seen simultaneously in the chorionic and basal plates. Thus, in the majority of cases where haemosiderosis was detected in the chorionic plate and/or basal plate, haemosiderosis was seen also in the membranes.

The extent and density of the haemosiderin deposition within the membranes varied between the three layers.

Based on the highest grade in the three layers of the membranes, haemosiderosis was mild in 54 cases (52.4%), moderate in 32 (31.1%), and severe in 17 (16.5%) (detailed data available from authors) (Fig. 1).

Three different patterns of haemosiderosis were distinguished: a cluster of blue spots, a blue ring around a cell and a dark blue big spot (Fig. 2). Two or all three patterns were seen in most cases (Table 1).

Clinical features of haemosiderosis

No significant relation was found between any of the obstetric complications and the presence of haemosiderosis (Table 2). There were no cases with abruption of the placenta or chorioamnionitis.

No significant relation was found between obstetric procedures and the occurrence of haemosiderosis. The majority of cases who had amniocentesis (12 versus 6; $p = 0.27$) or fetal scalp blood sampling (11 versus 3; $p = 0.48$) had haemosiderosis. There was one case with chorionic villous sampling, which did not have haemosiderosis. Fetal blood sampling and intrauterine transfusion was not performed in any of the 213 cases.

Haemosiderosis in the placenta was not related to maternal age, gravidity, parity, smoking or previous miscarriage or stillbirth. Placental haemosiderosis was not related to sex of the baby, low Apgar score or congenital abnormalities (Table 3). There was no correlation between haemosiderosis and gestational age: in the non-pathology

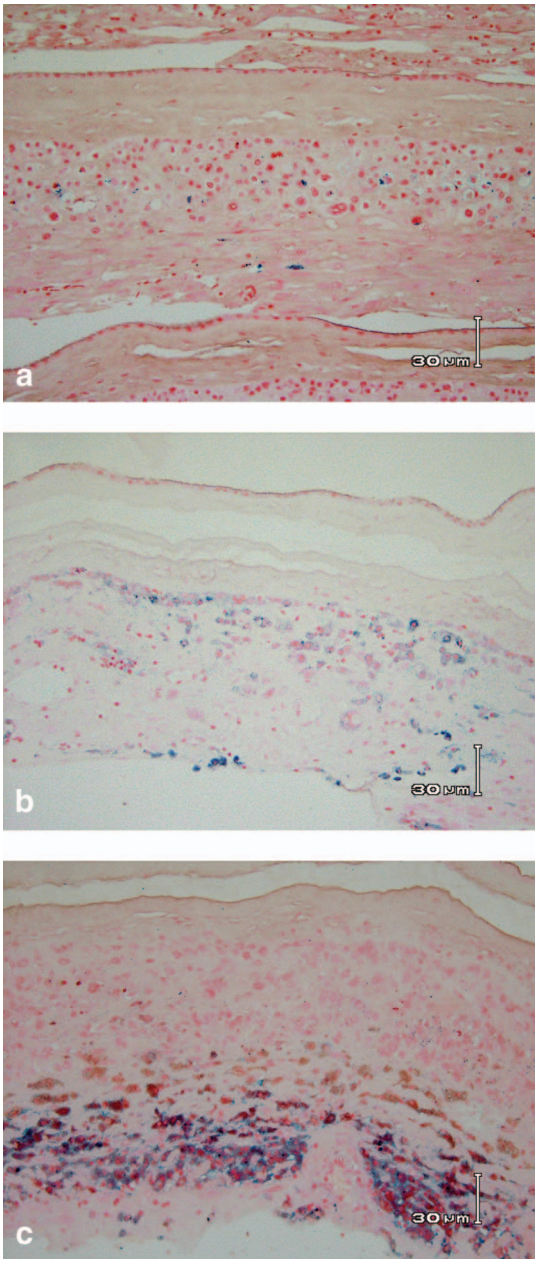

Fig. 1 Haemosiderosis in the membranes, demonstrating (a) mild, (b) moderate and (c) severe grades.

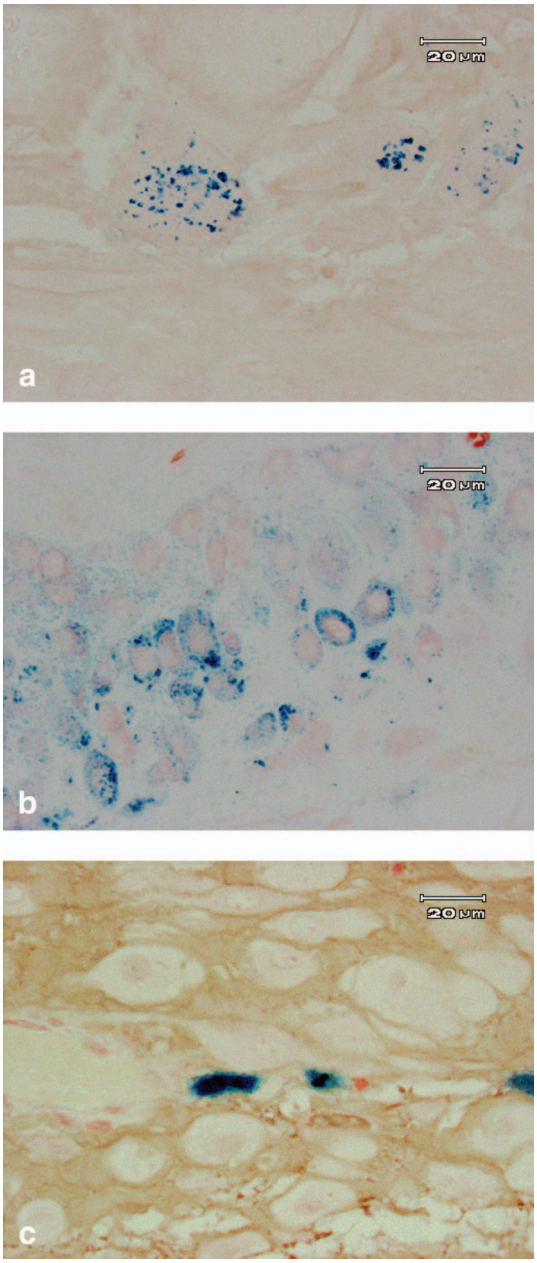

Fig. 2 Deposition of iron as (a) a clustered stippling of blue dots; (b) a ring around cells; and (c) a dark big spot.

Table 1 Pattern of haemosiderosis and topography

		Cluster of blue spots		Blue halo ring		Large dark blue spot	
	No. of cases	*n*	%	*n*	%	*n*	%
Amniotic layer of membranes	7	5	71.4	4	57.1	0	0.0
Chorionic layer of membranes	89	88	98.9	21	23.6	4	4.5
Decidual layer of membranes	49	27	55.1	35	71.4	9	18.4
Chorionic plate	18	11	61.1	4	22.2	13	72.2
Basal plate	18	15	88.3	8	44.4	18	100.0

Table 2 Correlation of obstetric complications and positive haemosiderin deposition in membranes, chorionic plate and/or basal plate of the placenta

		Haemosiderin positive		Haemosiderin negative		
	No. of cases	*n*	%	*n*	%	*p* value
Polyhydramnios	3	2	66.7	1	33.3	0.5248*
Oligohydramnios	1	1	100.0	0	0.0	0.5164*
Vaginal bleeding	12	5	41.7	7	58.3	0.6784
PPROM	30	16	53.3	14	46.7	0.9987
Previous PPROM	0†	–		–		–
Premature labour	52	28	53.8	24	46.2	0.7146
Previous premature labour	15†	6	40.0	9	60.0	0.6049
Abruption of placenta	0	–		–		–
Previous abruption of placenta	5†	3	60.0	2	40.0	0.4928*
Chorioamnionitis	0	–		–		–
Placenta previa	4	2	50.0	2	‘50.0	0.6641*
Gestational hypertension	3	0	0.0	3	100.0	0.1114*
Preeclampsia (moderate and severe)	19	12	63.0	7	37.0	0.4169
IUGR	14	7	50.0	7	50.0	0.8813
Previous IUGR	1†	1	100.0	0	0.0	0.4962
Caesarean section, elective or emergent	73	40	54.8	33	45.2	0.6030
Caesarean section (emergent)	54	32	59.3	22	41.7	0.2549
Previous caesarean section	23†	12	52.2	11	47.8	0.9684

*Based on one-tailed Fisher's exact test.
†Only multigravid patients: haemosiderin positive ($n = 66$), haemosiderin negative ($n = 67$).
IUGR, intrauterine growth restriction; PPROM, preterm premature rupture of the membranes.

indicated group, the median gestational age of the haemosiderosis positive group was 40 (range 34–42) weeks and of the haemosiderosis negative group was 39 (range 38–41) weeks; in the pathology indicated group, eight of 51 haemosiderosis negative placentas and 10 of 49 haemosiderosis positive placentas were <32 weeks ($p = 0.54$). Haemosiderosis occurred significantly less frequently in cases with thrombophilia ($p = 0.0496$), but the numbers were small. It was related to the observation of early decelerations during fetal heart rate monitoring (15 haemosiderin positive versus 5 haemosiderin negative; $p = 0.0498$). Other fetal heart rate abnormalities (late deceleration, variable deceleration, reduced variability, bradycardia, and tachycardia) were not significantly related to haemosiderosis. The majority of the cases with fetal distress (17/26; 65%) showed haemosiderosis in the placenta, but this was not significant. None of the babies was admitted to the neonatal intensive care unit (NICU).

No correlation was found between the obstetric and neonatal correlates and the grade, extent of haemosiderosis, density or pattern of haemosiderin staining.

Experiment

Haemosiderin was not found in any of the sections taken at various time intervals from both the blood contaminated and blood contamination-free halves of the placenta.

DISCUSSION

In this study we found haemosiderosis in the membranes and/or chorionic plate and/or basal plate in 51.6% (110/213) placentas examined. This figure was not significantly different between those 100 placentas that had an indication for pathological examination and those 113 that did not. Previous studies on diffuse chorioamniotic haemosiderosis had considerably lower incidences.[1,2,6] Redline and Wilson-Costello found an incidence of 2.2% (23/1023)[1] while Ohyama *et al*. found an incidence of 4.2% (46/1100).[2] In both of these groups there were indications for placental examinations but, even so, the incidence in our pathological examination-indicated placentas was 49/100. In a study on prematurity, decidual haemosiderosis was seen in 43% (196/462) preterm, which the authors defined as <32 weeks gestation, but in only 0.8% (1/108) term placentas.[6]

Table 3 Correlation of maternal and fetal clinical factors and positive haemosiderin deposition in membranes, chorionic plate and/or basal plate of the placenta

		Haemosiderin positive		Haemosiderin negative		
Clinical factors	No. of cases	*n*	%	*n*	%	*p* value
Mother						
Age (years)						
<20	14	8	57.1	6	42.9	0.8813
>34	45	23	51.1	22	48.9	0.9303
Primigravida	80	44	55.0	36	45.0	0.5361
Grand multiparous (P≥5)	2	1	50.0	1	50.0	0.7345*
Smoking (prior and/or during pregnancy)	47[†]	22	46.8	25	53.2	0.5579
Thrombophilia	7	1	14.3	6	85.7	0.0496*
Previous stillbirth	4[‡]	3	75.0	1	25.0	0.3359
Previous miscarriage	50[‡]	25	50.0	25	50.0	0.9171
Baby						
Male sex	106	50	47.2	56	52.8	0.2755
Fetal distress	26	17	65.4	9	34.6	0.2073
Monitoring abnormalities	73	41	56.2	32	43.8	0.4185
Early deceleration	20	15	66.7	5	33.3	0.0498
Late deceleration	10	5	50.0	5	50.0	0.5842*
Variable deceleration	40	22	55.0	18	45.0	0.7673
Reduced variability	14	9	64.3	5	35.7	0.4823
Bradycardia	14	7	50.0	7	50.0	0.8813
Tachycardia	14	6	42.9	8	57.1	0.6863
Meconium stained liquor	23	16	69.6	7	30.4	0.1095
Apgar score 0–3						
At 1 min	3	1	33.3	2	66.7	0.4752*
At 5 min	0	–		–		
Apgar score 4–7						
At 1 min	51	27	52.9	24	47.1	0.9585
At 5 min	9	3	33.3	6	66.7	0.2176*
Congenital abnormalities	9[§]	3	33.3	6	66.7	0.2176*
In gastrointestinal tract	1	0	0.0	1	100.0	0.4836*
Admission into NICU	0	–		–		–

*Based on one-tailed Fisher's exact test.
[†]Ten cases were unknown: five were haemosiderin positive and five were haemosiderin negative.
[‡]Only multigravid patients: 66 were haemosiderin positive, 67 were haemosiderin negative.
[§]Sixteen cases were unknown: seven were haemosiderin positive and nine were haemosiderin negative.
NICU, neonatal intensive care unit.

Given this marked difference in the incidences, firstly, we established that haemosiderosis was not an artefact of placental handling prior to placental sampling and processing. We then asked whether there were differences in the study designs. While our study included the basal plate, there was only one case in which haemosiderosis was seen solely in the basal plate but not concurrently in either the chorionic plate or membranes. Thus, our incidence of haemosiderosis in only membranes and/or chorionic plate, as in the design of the other two studies,[1,2] is still significantly greater than those observed by the previous investigators. Our choice of Perls' Prussian Blue stain for detecting iron compared with Gomori and Berlin Blue, as used by the other groups, is unlikely to explain the difference since the other two methods are variants of the Perls' stain. It is probable that selection of cases could account for some of the difference. Although those studies had seemingly large sample sizes, the selection of the cases excluded examination of many of those placentas for haemosiderosis.[1,2] In the former study, from 1023 placentas, 206 had pigment, of which 170 were excluded because of a history of meconium staining or a histological finding 'suggestive of meconium' and, thus, iron staining was only performed for 36 placentas.[1] This is significant as the differentiation between meconium and iron pigment on light microscopy alone can be extremely difficult.[7–10] In the latter study, the method infers that iron staining was performed following light microscopy determination of pigment in the membranes and chorionic plate.[2] In our study, we non-selectively applied the iron staining to one section of the membranes and one full thickness that included the basal plate and chorionic plate of all the placentas blinded to the naked eye appearance, clinical history or initial light microscopic evaluation.

We did not find haemosiderosis in the membranes, chorionic plate and/or basal plate of the placenta to be associated with maternal and/or fetal clinical factors of chronic separation of the placenta or with preterm birth. We are at a loss to explain the association between early decelerations during fetal heart rate monitoring and haemosiderosis, which was just statistically significant as was the negative correlation with thrombophilia; there was no significant relationship between fetal distress and haemosiderosis. Procedures that may lead to leakage of blood into the amniotic fluid might be anticipated to be related to haemosiderosis in the amniotic and chorionic layer of the membranes and/or chorionic plate. Although haemosiderosis was found more frequently in cases where either amniocentesis or fetal scalp blood sampling had been performed, this was not significant; umbilical blood sampling or intrauterine transfusion was not performed in any of the pregnancies studied.

A difficulty with the concept of diffuse chorioamniotic haemosiderosis is that the term 'diffuse' was not defined;[1,2] the absence of a definition of diffuse and whether localised lesions were differentiated and excluded in other studies could also account for the difference in the incidence between those studies and the current study. This difficulty is further compounded by an attempt to quantify the magnitude into categories of mild, moderate or severe.[1,2] Salafia *et al.* sorted placentas into either having haemosiderosis or not,[6] an approach which we also took. In quantifying haemosiderosis, we used objective criteria to define extent and density of the haemosiderin deposition. Using our definition, diffuse haemosiderosis was not correlated with any of the obstetric or neonatal characteristics. Furthermore, the pattern of staining did not appear to correlate with the obstetric or neonatal characteristics. The reasons for the different patterns of haemosiderin staining are unclear to us.

The distribution of iron staining within the membranes could have provided an insight as to the source of blood and haemosiderin. It could be speculated that where there was iron in the decidual or in the decidual and chorionic layers of the membranes, the direction of haemosiderin uptake in the membranes was from the decidual layer towards the amniotic cavity, and where there was iron in the amniotic or in the amniotic and chorionic layers of the membranes, the direction of haemosiderin uptake in the membranes could be from the amniotic layer towards the decidua. However, the results did not provide any conclusive insight into this direction and, indeed, the majority of haemosiderin positive membranes had haemosiderosis only in the chorionic layer. We suggest that a possible source of the haemosiderin could be explained by the embryology of the amniochorial membranes: prior to the fusion of the decidua capsularis with the decidua parietalis, the maternal vessels in the decidua capsularis contain blood and this blood supply becomes attenuated with enlargement of the chorionic sac, resulting in the creation of the smooth chorion laeve and fusion of the decidua capsularis with the decidua parietalis. Therefore, whether there is haemosiderin within the amniochorial membranes at delivery could be dependent on the amount of residua of blood within the chorion capsularis and decidua capsularis. The sources of haemosiderin in the chorionic plate and basal plate are likely to be retroplacental haemorrhage and intra-amniotic bleeding, respectively.

The lesion of placental haemosiderosis is poorly elaborated in the standard books of placental pathology[7–10] which quote the association with circumvallate placentation,[7–10] chronic haematoma[8,9] and intrauterine growth restriction.[8] It has also been found to be one of several placental lesions significantly associated with cerebral palsy and neurological impairment following term delivery.[11] Since placental examination is pivotal in medical legal cases, especially with regard to cerebral palsy and neurological impairment,[12] it was imperative that a critical re-examination of the clinico-pathological correlations and incidence of the lesion be performed. In conclusion, the incidence is markedly higher than previously reported and haemosiderosis is seen as frequently in placentas without an indication for pathological examination. However, haemosiderosis in the placenta is not due to an artefact of placental handling and we have not found it to be associated with chronic peripheral separation of the placenta or with adverse neonatal outcome. It is likely that haemosiderosis in the amniochorial membranes is physiological in the majority of cases. It remains to be determined which placentas displaying haemosiderosis have pathological causes for this.

Address for correspondence: Professor T. Y. Khong, SA Pathology, Women's and Children's Hospital, 72 King William Road, North Adelaide, SA 5006, Australia. E-mail: yee.khong@adelaide.edu.au

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