Original Article

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Villous Capillary Lesions Of Placenta: A Ten-Year Experience With Brief Review Of Literature

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ABSTRACT

Background: Villous capillary (VC) lesions of placenta range from reactive to benign tumors such as chorangiosis (CH), chorangiomatosis (CM) and chorangioma (CA). Associated with perinatal morbidity and mortality, these rare lesions are documented with maternal, placental and fetal risk factors. The aim of this study was to analyze the clinico-pathological profile of VC lesions of placenta and to compare the associated risk factors between VC lesion (CH) and those with no VC lesions.

Methods: This retrospective study includes all the VC lesions of Placenta diagnosed in Pondicherry Institute of medical sciences from January 2006 to February 2016. For comparison, gestational age matched controls with no VC lesions were obtained. Chi-square test or fischer's exact test was used for statistical analysis.

Results: Of 29 VC lesions of placenta (5.6%) in 10 years, 27 were CH. Commonly associated feto-maternal factors include anemia (47.4%), oligohydramnia (33.3%), infection (28.6%), pre-eclampsia (23.8%), NICU admission (47.8%), fetal growth retardation (17.4%), congenital anomaly (17.4%), intrauterine death (13%). When compared with controls, CH had significantly increased LSCS, premature rupture of membranes and histologically, chorioamnionitis and funisitis that support its infective etiology. One case of CA associated with IUGR, polyhydramnios was found to have CH in her next pregnancy which points to a possibility of genetic predisposition among VC lesions. CM was diagnosed in primi with severe pre-eclampsia and asymmetric IUGR.

Conclusion: Prevalence of CH is 5.2%. VC lesions of placenta are commonly associated with complicated pregnancy and neonatal morbidity.

Keywords: *Villus Capillary Lesions; Chorangiosis; Chorangioma; Chorangiomatosis*

Introduction

Placenta is a highly vascular, hemostatic organ derived from both maternal and fetal structures. Any complications, pre or post placental will get reflected on placental tissue that can easily be examined by light microscopy. One such condition is the villous capillary (VC) lesions of placenta that include chorangiosis (CH), chorangiomatosis (CM) and chorangioma (CA). These are interrelated conditions ranging from reactive to benign tumors. [1] They correlate with significant perinatal morbidity and mortality because of their associated maternal, fetal and placental risk factors. [2] These rare lesions are less widely studied except for few case reports.

The objective of this study is to document the clinico-pathological features of VC lesions of placenta and to compare the associated risk factors between cases with VC lesions and those with no VC lesions.

Materials and Methods:

This retrospective record based study was carried out in the department of pathology, Pondicherry institute of medical sciences, Pondicherrry. All the cases diagnosed as chorangiosis (CH), chorangioma (CA) and chorangiomatosis (CM) by histopathological examination from January 2006 to February 2016 were included in the study. The clinical details were retrieved from available case files and request forms. To know the significant clinical associations of VC lesions of placenta from those with no VC lesion, gestational age matched controls were obtained for comparison. Only CH cases were studied for comparative analysis, as CA and CM were too less in number.

CH is diagnosed as per Altshuler's criteria which " when inspection with a x10 objective showed 10 villi each with 10 or more vascular channels in 10 or more non-infarcted, non-ischemic zones of atleast three different placental areas". [2] Normally terminal villus has 2 to 6 capillary vessels even when represented twice in the section. [3, 4] CM is characterized by increase in villous capillaries that permeates normal villous structure. CA is a neoplastic proliferation of capillaries and stroma within a villous forming an expansile nodular lesion. [1]

For statistical analysis, Chi square test or Fischer's exact test was done using SPSS software to find the significant

variables between VC lesions and no VC lesions. P-value less than 0.05 was taken as statistically significant.

Results

There were total of 14,308 deliveries during the study period of 10 years, out of which 520 placentas (3.6%) were sent for histopathological evaluation. Among 520 placentas, Villous capillary (VC) lesions were diagnosed in 29 (5.6%) with 27 (5.2%) showing Chorangiosis (CH) and one each of Chorangioma (CA) and Chorangiomatosis (CM).

Majority of patients with CH were primi (15/25, 60%) aged between 22 and 41 years who delivered at more than 34 weeks (20/22, 90.9%) by lower segment cesarean section (LSCS), of which most had emergency LSCS (14/16, 87.5%). The most common clinical associations include maternal anemia and increased number of neonatal intensive care unit (NICU) admissions. Histologically, chorioamnionitis was seen in majority of placenta with CH.

Table 1 compares the clinical associations between CH and Non-VC lesions of placenta. Total number of deliveries by LSCS, premature rupture of membrane (PROM) and histological features of chorioamnionitis, funisitis were significantly higher in CH when compared to controls.

There was one case each of CM and CA in this study. CM was diagnosed in a 26-yr-old hypothyroid primi at term gestation with severe pre-eclampsia, intrauterine growth retardation (IUGR). She delivered a 1.7 kg male baby. Placenta showed features of diffuse multifocal CM with areas of infarction and calcification.

The other case was 22-year-old primi with polyhydramnios and severe IUGR, delivered a 1.8 kg male baby by LSCS at 36 weeks. Antenatal USG at 34 weeks revealed two hypoechoic lesions in placenta, suggestive of CH. Grossly placenta showed two nodular mass measuring 7.5x6.5x4.5 and10.5x7x6, one with attached pedicle. Histology showed CA in both nodules with evidence of infarction in one of them (previously published as a case report from our institute). [5] Interestingly, in her next pregnancy placenta showed evidence of CH. She was admitted at 38 weeks then with leaking per vaginum and underwent emergency LSCS for non-progression of labour and brow presentation.

Table 1: Comparison of clinical and histological associations between Chorangiosis (CH) and non-Villous capillary lesions.

VARIABLES	Villous capillary lesion (CH)	%	Non-Villous capillary lesions	%	p value
ANTENATAL VARIABLES:	n=27		n=42		
Number of Primi gravida	15 (of 25)	60	20	47.6	0.520
Number of twin pregnancy	2	7.4	5	11.9	0.69
Number of LSCS	16 (of 22)	72.7	19	45.2	0.036
MATERNAL FACTORS:	n=21		n=42		
Anemia	9 (of 19)	47.4	16 (of 39)	41	0.770
Oligohydramnios	7	33.3	11	26.2	0.554
Fever &/ infection	6	28.6	6	14.3	0.173
Premature rupture of membrane	5	23.8	2	4.8	0.02
Pre-eclampsia	5	23.8	5	11.9	0.28
Gestational Diabetes Mellitus	3	14.3	7	16.7	0.806
Hypothyroidism	2	9.5	4	9.5	0.465
FETAL FACTORS:	n=23		n=47		
NICU admissions	11	47.8	17	36.2	0.350
Congenital anomaly	4	17.4	3	6.4	0.149
Intrauterine growth retardation (IUGR)	4	17.4	8	17	0.9
Intrauterine death	3	13	16	34	0.06
HISTOLOGICAL FEATURES:	n=29		n=47		
Chorioamnionitis	11	37.9	5	10.6	0.005
Calcification	9	31	28	59.6	0.016
Infarction	6	20.7	13	27.7	0.750
Funisitis	2	6.9	0	0	0.036

Table 2: Various studies and case reports on risk factors associated with Chorangiosis (CH).

Author, year, no. of cases	Maternal factors	Fetal factors	Placental factors	Histology
Franciosi et al, [8] 1999, n=2	LSCS	Fetal distress, Intrauterine death (IUD)	Abruptio placenta, Tight nuchal cord	CH
Ogino et al, [1] 2000, n=46	Diabetes, Pre-eclampsia, Multiple pregnancy	IUGR, congenital anomaly	Placentomegaly	CH, Delayed villous maturation, Villitis of unknown etiology
Ossa et al, [11] 2001, n=1	Pre-eclampsia	-	-	CH
Gupta et al, [12] 2006, n=12	Syphilis, Pre-eclampsia, Diabetes, jaundice	Still born, non-immune hydrops	Abruptio placenta	CH, infarction, calcification
Mathew et al, [9] 2008, n=2	Pleural Tuberculosis, LSCS	Fetal distress	Single umblical artery	CH
Agale et al, [7] 2009, n=3	Severe anemia, Pre-eclampsia, LSCS	IUD , congenital anomaly, fetal distress	Abruptio placenta	CH
Soma et al, [10] 2012, n=58	LSCS, HELLP syndrome	Low birth weight, congenital anomaly, IUGR, IUD	Single umblical artery	CH, infarction, Intervillous thrombosis
Malathi et al, [13] 2014, n=1	Pre-eclampsia	IUD	-	CH
Aparna et al, [6] 2014, n=2	Pre-eclampsia, anemia, LSCS	Fetal distress	-	CH
Srinivasan et al, [3] 2014, n=10	Anemia, Diabetes, hypothyroid, Pre-eclampsia	Not available	-	CH
Present study, 2016, n=27	LSCS, Anemia, oligohydramnios, infection, Pre-eclampsia, pre-mature rupture of membrane, Diabetes, hypothyroid	Fetal distress, IUGR, congenital anomaly, IUD	-	CH, chorioamnionitis, calcification, infarction, funisitis

Table 3: Various studies and case reports on risk factors associated with Chorangiomatosis (CM).

Author, year, no. of cases	Maternal factors	Fetal factors	Placental factors	Histology
Ogino et al, [1] 2000, n=39	Pre-eclampsia, Multiple pregnancy, diabetes	IUGR, congenital anomalies	-	Focal CM, segmental CM, diffuse CM
Chopra et al, [16] 2006, n=1	LSCS	Non-immune hydrops, intestinal stenosis	-	Diffuse Multifocal CM
Bagby et al, [14] 2010, n=53	Advanced age*, non-primi gravida*	Congenital anomalies*	-	Diffuse Multifocal CM, Avascular villi, Distal villous immaturity
Perera et al, [17] 2011, n=1	Twin gestation	IUGR, hydrops, anemia		Diffuse Multifocal CM
Kalli et al, [15] 2012, n=1	Positive chlamydia screen	Still born, congenital anomaly	-	Diffuse Multifocal CM
Boroujeni et al, [18] 2014, n=105	-	Low birth weight*, NICU* admission	-	Diffuse Multifocal CM, focal CM
Present study, 2016, n=1	Severe pre-eclampsia	IUGR, NICU admission	-	Diffuse Multifocal CM

*Significant clinical association

Table 4: Various studies and case reports on risk factors associated with Chorangioma (CA).

Author, year, no. of cases	Largest dimension (cm)	Maternal factors	Fetal factors	Placental factors	Histology
Chen et al, [22] 1997, n=2	9	Polyhydramnios, preterm labour, Premature rupture of membrane	Anemia, thrombocytopenia, hemangiomatosis	-	CA with mesenchym-al hyperplasia
Ogino et al, [1] 2000, n=36	Not available	Multiple pregnancy, Pre-eclampsia	IUGR, cong anomalies	Placenta <10th percentile weight	Nodular CA, multi-nodular CA
Lez et al, [23] 2010, n=1	7	-	-	-	CA
Adil et al, [20] 2012, n=1	13	Pre-eclampsia, LSCS	Low birth weight	-	CA
Kodandapa-ni et al, [19] 2012, n=1	12	Polyhydramnios, preterm labor	Low birth weight, died of DIC	-	CA
Tihonenko I, [24] 2012, n=1	3	-	Hydrops, cardiac failure, anemia	-	Multiple CA
Lokuhatty et al, [25] 2014, n=1	13	Polyhydramnios, preterm labor	IUGR, breech, NICU admission	-	CA with ischemic necrosis
Andola et al, [26] 2014, n=4	23	Preterm delivery, polyhydramnios, Pre-eclampsia	IUGR, Intra uterine death	Abruptio placenta	CA
Abdalla et al, [27] 2014, n=1	5	Polyhydramnios, anemia	-	-	CA
Srinivasan et al, [3] 2014, n=2	2.5	Pre-eclampsia, anemia	Not available	-	CA
Singh et al, [28] 2015, n=1	Not available	Polyhydramnios	IUGR	-	CA
Sahu et al, [29] 2016, n=1	7	Polyhydramnios	-	-	CA with infarction
Present study, 2016, n=1	10.5	Polyhydramnios, LSCS	IUGR, NICU admission	-	Of two CA, one shows infarction

Discussion

Placenta is a highly vascular organ involving vasculogenesis and angiogenesis in its development. In the third trimester, terminal villi are developed from the intermediate villi along with capillary loops that represent fetal vessels. Each capillary loop supplies 3 to 5 terminal villi and is sinusoidally dilated in such a way that it reduces the blood flow resistance. This process completes by 28 week. Terminal villous usually contains 2 to 6 capillaries occupying majority of cross section of terminal villi. Any factor that affects angiogenesis of placenta whether maternal or fetal will affect the number of capillaries per villi resulting in VC lesions. [3] In other words, VC lesions are thought to be an adaptive response to injury caused by various associated pre and post-placental risk factors.

Chorangiosis (CH): The prevelance of chorangiosis ranges from 5 to 6%. [2, 6] Most cases occur at term. [6, 7] In a study by Ogino et al, there were no cases of CH diagnosed before 32 weeks and were more than 10-fold common than CA. In the present study, CH is found in 5.2% of placenta with majority at more than 34 weeks and they are more than 20-fold common than either CA or CM.

CH is a diffuse process of hyper vascularity involving terminal villi.

It is thought to be a local adaptation to increase fetal access to maternal oxygen at interhemal membrane. Hypercapillarization may be due to excessive capillary looping due to decoupling stromal and vascular growth. [1] Chorangosis should be differentiated from congestion where the number of capillaries remains normal. [3, 8]

Risk factors associated with Chorangiosis: There are many maternal, fetal and placental factors associated with chorangiosis that are documented in literature. [1, 6, 8-10] They are:

Maternal disorders - pre-eclampsia, eclampsia, diabetes, infection (syphilis, UTI), anemia, smoking, jaundice, drug ingestion

Fetal factors - IUD, IUGR, congenital anomalies, apgar score <5

Placental lesions – abruption placenta, placenta previa, amnion nodosum, villitis (due to rubella,syphilis, Bortenella, CMV infection), umblical cord anomalies, placentomegaly

Table 3 shows clinico-pathological profile of CH in various recent studies. [1, 3, 6-13] Many feto-maternal factors in the present study correlate with the literature. Rare associations include Tuberculosis, hypothyroidism, oligohydramnios and PROM. So far only one case report each of tuberculosis [9] and hypothyroidism [3] were documented in CH. Also, associations with oligohydramnios and premature rupture of membrane were not reported previously.

To know the clinical significance of associated risk factors in CH, we compared with control placentas without VC lesions. Since majority of placenta in the study group were beyond 34 weeks of gestation, we took controls that were gestational age matched. After statistical analysis, we found patients with CH have significant increase in number of LSCS, PROM, Chorioamnionitis and funisitis than controls. (Table 1) Increased incidence of LSCS implies fetal &/ maternal complications that occurred acutely during delivery while the associations of PROM, chorioamnionitis and funisitis can be attributed to an underlying infective process.

Hypotheses Associated with Chorangiosis: Exact etiology of CH is unknown. There are various hypothesis described, common among them is hypoxia due to its association with anemia, smokers, high altitude and twin gestation. [1, 10] CH in the present study included two-twin pregnancy and 9 (47.4%) anemic patients. The other hypothesis is related to increased intamural pressure due to venous obstruction at umblical cord or fetal cardiac level. There were no placental factors documented in the present study. An alternative proposal is the associated infection (e.g, bacillary angiosis secondary to *bartonella sp*) with increase in local macrophage and its related cytokines like tumor necrosis factor –α. [1, 8] Ogino et al noted increased occurance of villitis in placentas with CH. [1] The present study showed increased incidence of antenatal infections with significant association of PROM, which would have lead to increased number of chorioamnionitis and funisitis (Table 2). Our study correlates more with the infective etiology of CH.

Chorangiosis has been documented even in normal pregnancy. [3] Our study did not include placentas from normal pregnant ladies with no risk factors. The other limitation is the difficulty in interpretation of capillarisation when it is collapsed which depends on mode of delivery, cord clamping, fixatives and time taken to fix the tissue after cessation of umblical circulation. [3]

Chorangiomatosis (CM): Uncommon among VC lesions, CM is a heterogenous, less well-defined lesion with features intermediate between CA and CH. [1, 10, 14] According to Ogino et al, CM shows capillary proliferation involving stem villi surrounding the central core and does not form expansile nodular lesion, however they permeate normal villous structure. [1] CM can be focal (confined to 1 to 5 villous cross sections), segmental (>5 contiguous villous cross sections) or diffuse multi-focal (multiple independent areas of placenta). [1] Diffuse multifocal CM usually presents with extreme prematurity (<32 weeks) and are associated with IUGR. [15]

Table 3 lists recent case studies and case reports of clinical associations [14-18] along with the present case of CM. Like CH, CM is associated with feto-maternal complications, common being prematurity, IUGR, pre-eclampsia. [16] In the study by ogino et al, [1] CM is significantly associated with multiple pregnancy and pre-eclampsia while the diffuse multifocal type correlated with increased number of IUGR and congenital malformations than controls. The one case of diffuse multifocal CM in the present study had associated pre-eclampsia with IUGR baby. CM is thought to represent abnormal capillary proliferation related to feto-placental developmental anomalies and abnormal fetal blood flow. [14]

Chorangioma (CA): CA is the most common benign tumor of placenta, analogous to hemangioma elsewhere with incidence of <1%. [3, 4, 19] Their usual location in the placenta is either marginal or subchorionic with gestational age between 32 to 36 weeks. [1] It presents either as expansile nodular mass or an incidental finding at microscopic examination of placenta. CAs are subtyped into nodular and mutinodular. Microscopic features of both include proliferating capillaries, intervening stroma comprised of fibroblast, macrophages, collagen and surrounding trophoblast. [1, 4] Occasionally CA can undergo infarction and degenerative changes like hyalinization, myxoid stromal change and calcification. [20] The three histological patterns described by Marchetti were angiomatous, cellular and degenerate, the most common being angiomatous pattern. [19, 21] Placenta of the present case showed two nodular masses measuring more than 5cm each and histology showed angiomatous type of CA with one showing evidence of infarction.

CA less than 5cm usually go unnoticed without any complications. But larger tumors more than 5 cm, called giant CA, acts as an arterio-venous shunt and cause

distinctive maternal and fetal complications. [22] The incidence of giant CA ranges from 1:3000 to 1:9000 births. [4, 20] Maternal complications include pre-eclampsia, placental abruption, polyhydramnios, preterm delivery and premature rupture of membrane. [3, 4] Fetal complications exclusive of giant CA are congestive heart failure, hydrops, hemolytic anemia, thrombocytopenia, congenital anomalies and IUGR. [19]

Table 4 highlights the associated complications of CA in various studies in the recent literature. [1, 20, 22-29] The most common of these complications causing perinatal morbidity are polyhydramnios and preterm delivery, the later being the result of hydramnios. [19] The present study case of giant CA also had polyhydramnios with associated IUGR. The causes of polyhydramnios are multifactorial. It can be because of transudation of fluid into amniotic cavity from the larger vascular area of CA or due to increased intravascular pressure caused by tumor obstructing the vessels near umblical cord insertion or because of functional placental insufficiency due to shunting of blood into the chorangial vascular bed. [25, 27] Also, Giant CA acts as physiological dead space leading to chronic hypoxia resulting in fetus growth restriction. [20]

Though CA is grouped under benign tumor, they are often thought to be hamartoma or hyperplastic capillary lesion. [20] Several possible etiologies were hypothesized: origin at very early gestation, primary stem villi origin, hypoxia and genetic predisposition [1]. In the present study case, occurrence of CH in present pregnancy following CA in previous pregnancy in the same patient supports genetic predisposition.

CH vs CM vs CA: Though VC lesions are related entities, they are distinct in their presentation and microscopic features. According to Ogino et al, multiple pregnancy and preeclampsia were found to be more common in CM and CA than CH. [1] Histologically, capillary proliferations in CM involve stem villi sparing the terminal villi, while capillaries in CH involve terminal villi sparing the stem villi.

To summarize, occurrence of CH is 20-fold more common than CM or CA with prevalence of 5.2%. Similar to other studies, VC lesions of placenta are commonly associated with complicated pregnancy and neonatal morbidity. When compared with gestational age matched controls, cases with CH showed significant increase in number of LSCS deliveries, PROM, chorioamnionitis and funisitis that supports the infective etiology of CH. Occurrence of CH in a patient with CA in her previous pregnancy reinforces the genetic predisposition among VC lesions. Knowledge on minute distinctions among VC lesions of placenta is essential for accurate diagnosis.

Conclusion

Thus placental pathology gives important information on the nature of injury it has sustained, as it is a sole organ of contact between mother and fetus. Henceforth, we recommend complete placental examination whenever indicated not only for diagnosis, but also to understand the evolution of the disease process.

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