Chronic villitis of unknown aetiology: Association with adverse pregnancy outcomes in a high-risk population in South Africa

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Abstract
Objective: Chronic villitis of unknown aetiology (CVUE) has been reported in association with adverse pregnancy outcomes, i.e. intra-uterine growth restriction (IUGR), preterm delivery and intra-uterine foetal death. The index study planned to describe associations between CVUE and clinical factors, including adverse pregnancy outcomes.
Methods: A retrospective, descriptive study of all of 92 cases of CVUE diagnosed during a 5-year period at a tertiary referral hospital.
Results: Forty-seven cases of CVUE (47/92) were classified as low grade, 42/92 as high grade and 3/92 as villitis, ungradable. Preterm birth was seen in two-thirds of cases (61/92; 66%). Thirty-eight cases (38/92; 41%) were associated with stillbirth. High grade CVUE had a statistically significantly greater association with stillbirth than low grade CVUE (p=0.019). Nearly half of the cases (42/92; 46%) were associated with IUGR.
Conclusions: In this cohort of chronic villitis in a low- and middle-income country high grade CVUE showed a statistically significant association with stillbirth compared to low grade CVUE.

Keywords
Placenta, villitis, chronic villitis of unknown aetiology, stillbirth, foetal growth retardation

Introduction

Chronic placental villitis is characterized by mononuclear inflammatory cells within chorionic villi (Figure 1).[1,2] In the vast majority of cases of histological villitis a specific infective organism cannot be identified[1], but when present, organisms of the so-called TORCH group (i.e. Toxoplasma gondii, rubella, cytomegalovirus [CMV], herpes simplex, syphilis and others) are frequently implicated. Non-infectious cases are designated, by exclusion, as chronic villitis of unknown aetiology (CVUE).[1] CVUE is a relatively common chronic inflammatory lesion of the placenta reported to occur in 5-15% of all third trimester pregnancies, and is distinctly uncommon prior to 32 weeks' gestation.[2-4] These widely differing incidences have been attributed to differences in sampling, diagnostic criteria, and the population from which the placentas were obtained.[5] Most recent studies support the hypothesis that CVUE is caused by an immune-mediated graft-versus-host type reaction mediated by maternal T-lymphocytes and activated resident foetal macrophages (Hofbauer cells).[1,2,4,5]

Although overlap with infectious villitis exists, the clinical and

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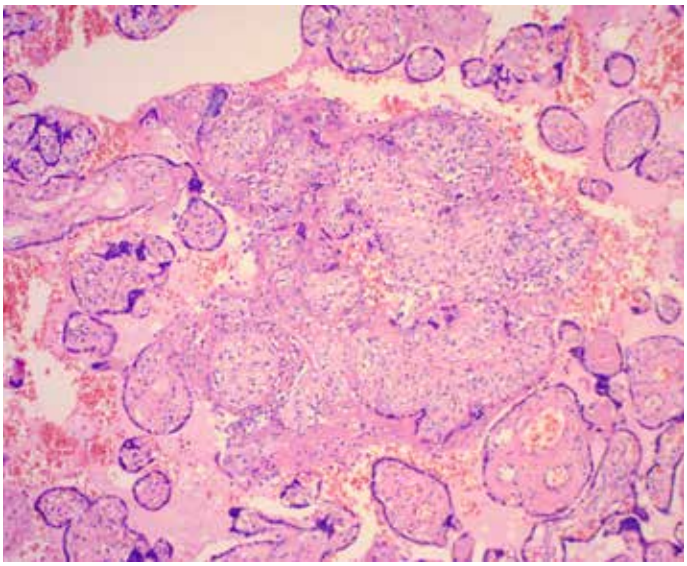
Figure 1. High grade CVUE. Lymphocyte-predominant inflammation involving more than 10 contiguous villi (haematoxylin-eosin, original magnification X100).



histological characteristics of CVUE are distinct.[2] CVUE typically lacks features typical of chronic infectious placentitis, such as uniform involvement of villi, a predominance of histiocytes and plasma cells, villous oedema, fibrosis, mineralization and prominent inflammation of the foetal membranes and umbilical cord.[2,6,7]

Although CVUE may be of no clinical significance, especially when low grade, focal and confined to terminal villi, CVUE has been reported in association with adverse pregnancy outcomes including intra-uterine growth restriction (IUGR), preterm birth, intra-uterine foetal death (IUFD), neurological injury, maternal pre-eclampsia, hypertension and obesity.[2,4,5,8,9] In addition, CVUE, especially when high grade and diffuse, has a 10-50% risk of recurrence in subsequent pregnancies, often in a more severe form, or as chronic histiocytic intervillositis.[2,4,10,11] Women with recurrences are especially prone to severe foetal IUGR, premature delivery and IUFD.[4]

Methods

Tygerberg Hospital is a tertiary referral academic centre with approximately 7000 deliveries annually. We conducted a retrospective descriptive study of placentas delivered at Tygerberg Hospital in which chronic villitis was diagnosed over a 5-year period. The aims of this study were to 1. determine the frequency of CVUE in the study population; 2. determine the severity (i.e. grade of villitis) and pattern of villous involvement in cases of CVUE; 3. describe associations between the histopathological findings and clinical outcomes including IUGR, stillbirth and preterm birth in cases of CVUE.

During the study period there were 35 076 deliveries of babies with birth weights exceeding 500g. Of these, 2179 placentas (6.2%) were received at the Division of Anatomical Pathology of mothers who delivered at Tygerberg Hospital.

At Tygerberg Hospital placentas are selectively submitted for histopathological evaluation following adverse maternal or perinatal outcomes according to an agreed protocol (Table 1).

Cases of CVUE were identified from among all the placentas submitted to the Division of Anatomical Pathology, Tygerberg Hospital over a 5-year period (from 1 January 2010 through 31 December 2014). Maternal and perinatal data of these placentas with CVUE were revisited for associations between CVUE and specific adverse clinical events.

The electronic Disalab histopathology database at the Division of Anatomical Pathology, Tygerberg Hospital, National Health Laboratory Service and Stellenbosch University was searched for the term "villitis" during the time period 1 January 2010 through 31 December 2014. Placentas submitted from other health care centres were excluded.

Chronic villitis was designated as mononuclear inflammation predominantly localized to the stroma of villi, with allowance of some extension into the adjacent intervillous space. CVUE was defined as chronic villitis for which an infectious cause could not be identified by either clinical means, i.e. routine ante- or perinatal serology, or histologically, i.e. examination of haematoxylin and eosin-stained slides, histochemical stains or immunohistochemical stains for CMV, *Treponema pallidum* and *Toxoplasma gondii*, when indicated.[12] Placentas of mothers with a positive serologic test(s) for syphilis were designated as congenital syphilis.

Cases with an initial diagnosis of chronic villitis or in which a diagnosis of villitis was uncertain were retrieved from the pathology laboratory archive, assigned a study number and entered onto a password protected computer document. Ethics approval for this research project was obtained from the Health Research Ethics Office at Stellenbosch University (reference: S15/09/200).

Placental Data

Each case consisted of one glass slide with a haematoxylin and eosin (H&E)-stained section of the umbilical cord and foetal membranes, and a minimum of three sections of the placental parenchyma. These cases where reviewed by two pathologists (PS and VP) and reclassified as i. no villitis or ii. chronic villitis (either low or high grade), each with or without chorioamnionitis. Cases without histological evidence of villitis were excluded from the study.

Table 1. Indications for placental histology at Tygerberg Hospital

1	Unexplained stillbirth ≥24 weeks or ≥500g, excluding cases of abruptio placentae and cord prolapse. In cases of uncertainty the placenta should be retained with the body, for opinion by a clinical geneticist.
2	Signs of asphyxia in a viable baby, including all neonates who required resuscitation (excluding abruptio placentae or cord prolapse).
3	Unexplained mid-trimester losses >16 weeks.
4	Idiopathic preterm labour (gestational age <34 weeks or birth weight <1800g).
5	Clinically suspected chorioamnionitis.
6	Severe intra-uterine growth restriction without antenatal work-up, i.e. Doppler investigations and ultrasound, unless otherwise requested by the Foetal Medicine team.
7	Multiple pregnancies: a. All indications relevant to singleton pregnancies. b. All multiple pregnancies with uncertain chorionicity and growth discordance, or perinatal morbidity/ mortality.
8	Congenital abnormalities without prior diagnosis, unless otherwise requested by the clinical genetics or Foetal Medicine team.
9	Severe preeclampsia (only if requested by the Special Care Unit).
10	Mothers with active tuberculosis on antituberculosis therapy, or with clinical indicators of maternal tuberculosis.

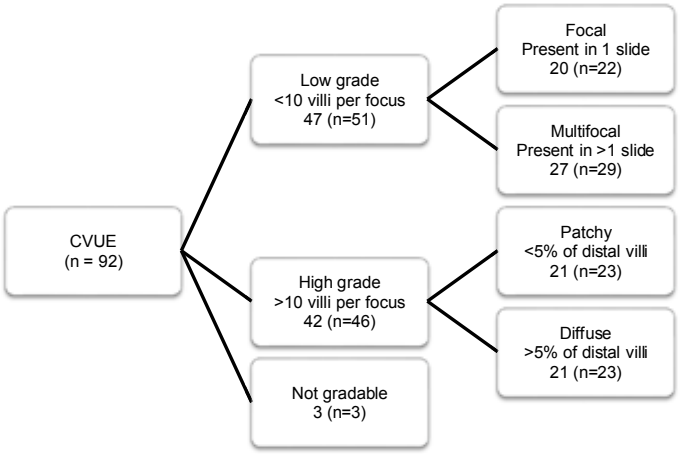
The following histological parameters were assessed and classified according to the Amsterdam Placental Workshop Group Consensus Statement recommendations.[12] CVUE was classified according to the predominant inflammatory infiltrate as lymphohistiocytic or lymphoplasmacytic, and graded as i. not gradable, possible low grade; ii. not gradable, possible high grade; iii. low grade, focal; iv. low grade, multifocal; v. high grade, patchy; or vi. high grade, diffuse (Figure 2). The pattern of distribution of the chronic villitis was classified as i. subchorionic (upper third of parenchyma); ii. parabasal/paraseptal (predominantly involving anchoring villi embedded in the basal plate and adjacent terminal villi), or iii. randomly distributed throughout the parenchyma.[12] Placentas were assessed for an additional diagnosis.

Reviewers were blinded to all clinical information except gestational age. In cases where uncertainty or disagreement existed between the original diagnosis and the diagnosis made at review, a consensus opinion was reached after combined review and discussion with an additional pathologist (CAW).

Clinical Data

Maternal and obstetric data was obtained by a perinatal clinician

Figure 2. Histological grading of villitis (n=92).



CVUE, chronic villitis of unknown aetiology.

(DM) and registered nurse from archived obstetric records, patient files and the Perinatal Problem Identification Program.[13] The clinical parameters assessed are listed in Table 2.

Preterm birth was designated as birth before 37 completed weeks of gestation. Newborn weights (as measured at birth) were classified as intra-uterine growth restriction (<10th percentile), adequate for gestational age (10th to 90th percentile), large for gestational age (>90th percentile) or unknown (if weight was not known, or gestation <20weeks). For pregnancies up to 35 weeks and 6 days' gestation, IUGR was calculated based on estimated foetal weight using non-gender specific Salomon graphs.[14] Birth weights for pregnancies at 36 completed weeks onwards were classified according to gender specific INTERGROWTH charts.[15] For the purpose of this study, stillbirth was defined as IUFD that occurred at or after 20 completed weeks of pregnancy. One case of IUFD occurred at <20 weeks' gestation, i.e. at 17 weeks. Neonatal death was designated as infant death within the first 28 days of life after live birth. The follow-up period for adverse neurological outcome was six months.

Table 2. Clinical parameters assessed

Maternal	Obstetric	Foetal
Gravidity	Singleton/multiple pregnancy	Preterm birth[b]
Advanced maternal age	Gestational age	Stillbirth[c]
Obesity[a]	Mode of delivery	Neonatal death[d]
HIV status		Intra-uterine growth restrictione
Hypertension/ preeclampsia		Adverse neurological outcomes[f]
Cigarette smoking		

[a]Body mass index categories were defined as normal weight (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2), obese (30-39.9 kg/m2) and morbidly obese (>40 kg/m2).
[b]Preterm birth was designated as birth before 37 completed weeks of gestation.
[c]Stillbirth was defined as foetal death at or after 20 completed weeks of gestation.
[d]Neonatal death was defined as infant death within the first 28 days of life after live birth.
[e]Intra-uterine growth restriction was defined as weight <10th percentile.
[f]Abnormal neurological outcomes include neonatal encephalopathy (i.e. disturbed neurologic function in the earliest days of life manifested by a subnormal level of consciousness, seizures or depression of tone and reflexes), cerebral palsy or closely related, non-progressive motor disorder in live born infants as determined by a paediatrician and documented in the patient's medical records in the first six months of life.

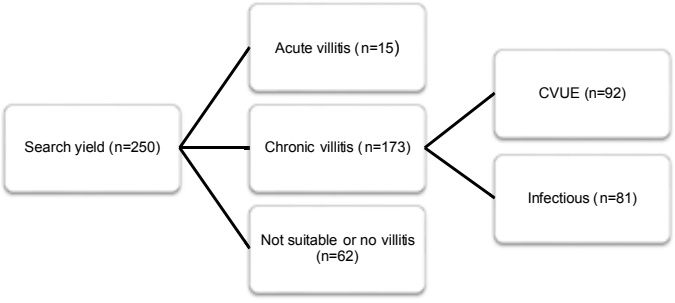
Statistical analysis

Simple descriptive statistical analysis was performed. Data were captured in Excel, cleaned and imported to Statistica (v.13, Statsoft) for analysis. Normality of data was assessed using the Kolmogorov-Smirnov (K-S) normality test with Lilliefors correction and normal distribution confirmed with the Shapiro-Wilk test. Data that were normally distributed is presented as mean ± standard deviation (mean±SD) whereas non-parametric data are presented as median and interquartile ranges (25th-75th percentiles). Categorical data were described using frequencies and proportions. Associations between histological and clinical outcomes were determined using chi-square or Fisher's exact tests, where appropriate. Level of significance was accepted at $p<0.05$.

Results

The electronic search yielded 250 cases classified by initial pathological assessment as i. villitis uncertain (22/250) (n/N); ii. acute villitis (15/250) (n/N); iii. chronic infectious villitis (81/250) (n/N); iv. chronic non-infectious villitis (124/250) (n/N) or v. not suitable (8/250) (n/N). An identifiable infectious cause was identified in 7 of 15 cases of acute villitis, i.e. syphilis (n=2), mycobacterial infection (n=3), Gram positive bacteria (n=1) and Gram-negative bacteria (n=1). Upon histopathological review cases were reclassified as i. not suitable (62/250) (n/N); ii. acute villitis (15/250) (n/N), or iii. chronic villitis (173/250) (n/N), of which 81 cases (81/173) (n/N) (46.8%) with an identifiable infectious cause, i.e. congenital syphilis (n=74), mycobacterial infection (n=1), CMV (n=4) and unclassified viral TORCH-type infection (n=2), were excluded from the study. The remaining 92 cases were designated as CVUE (Figure 3).

Figure 3. Classification of villitis after review (n=250).



CVUE, chronic villitis of unknown aetiology.

Table 3. Clinical parameters in low and high grade villitis.

Maternal factors				
	Low grade CVUE (n = 47)	**High grade CVUE (n = 42)**	**Overall demographics[a] (n=92)**	**P value**
Gravidity (G)	G1 n=12 (26%) G2 n=16 (34%) G3 n=8 (17%) G4 n=4 (8%) G5 n=7 (15%)	G1 n=9 (22%) G2 n=11 (26%) G3 n=9 (21%) G4 n=7 (17%) G5 n=2 (5%) G6 n=2 (5%) G7 n=1 (2%) Not reported n=1 (2%)	Median: 2 Interquartile range: (2-4)	p=0.27
Advanced maternal age (>35 years)	n=9 (19%)	n=8 (20%)	Age distribution: <20 years: n=8 (9%) 20-24 years: n=23 (25%) 25-34 years: n=43 (47%) 35-39 years: n=12 (13%) >40 years: n=5 (5%) Not reported: n=1 (1%)	p=0.48
Obesity (BMI>30kg/m2)	n=8 (17%)	n=7 (17%)	BMI distribution[b]: Normal weight: n=16 (17%) Overweight: n=11 (12%) Obese: n=12 (13%) Morbidly obese: n=4 (4.5%) Not reported: n=49 (53.5%)	p=0.22
HIV positive	n=4 (10%)	n=4 (10%)	HIV status: Negative: n=75 (82%) Positive: n=10 (11%) Not reported: n=7 (8%)	p=0.94
Hypertension/ preeclampsia	Preeclampsia n=8 (67%) Chronic hypertension n=3 (25%) Chronic hypertension with superimposed preeclampsia n=1 (8%)	Preeclampsia n=8 (53%) Chronic hypertension n=3 (20%) Chronic hypertension with superimposed preeclampsia n=3 (20%) Gestational hypertension n=1 (7%)		
Cigarette smoking	n=9 (25%)	n=11 (31%)	Smoking status: Yes: n=20 (22%) No: n=55 (60%) Not reported: n=17 (18%)	p=0.60
Pregnancy factors				
	Low grade villitis (n = 47)	**High grade villitis (n = 42)**	**Overall demographics[a] (n=92)**	
Mean gestational age at delivery (weeks)	33	34	Median (25th-75th percentile) 35 (31-37) weeks	p=0.43
Mode of delivery	Vaginal n=28 (60%) Emergency Caesarean section n=18 (38%) Elective Caesarean section n=1 (2%)	Vaginal n=22 (52%) Emergency Caesarean section n=14 (33%) Elective Caesarean section n=4 (10%) Not reported n=2 (5%)		

[a]Overall demographics calculated for CVUE overall, i.e. low grade CVUE, high grade CVUE and villitis, ungradable (n=92).
[b]Body mass index categories were defined as normal weight (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2), obese (30-39.9 kg/m2) and morbidly obese (>40 kg/m2).
CVUE, chronic villitis of unknown aetiology.
ns, not significant. Level of significance accepted at p<0.05

Upon grading the severity of CVUE, 47 cases (47/92; 51%) were classified as low grade, 42 (42/92; 46%) as high grade and 3 (3/92; 3%) as villitis, ungradable (Figure 2). The inflammatory cell infiltrate was predominantly lymphohistiocytic in 83 cases (83/92; 90%) and lymphoplasmacytic in 9 cases (9/92; 9.8%). All grades of villitis showed a random distribution of the inflammatory infiltrate within the placental parenchyma.

Of the 92 cases of CVUE, 58 (58/92; 63%) had an additional diagnosis, i.e. 33 (33/58; 57%) maternal vascular malperfusion; 6 (6/58; 10%) abruptio placentae; 14 (14/58; 24%) chorioamnionitis, and 5 other diagnoses (5/58; 9%).

Selected clinical variables and their frequencies in cases with low and high grade CVUE are presented in Table 3. There were no significant differences between low and high grade villitis in their association with the clinical variables studied.

The number and frequency of all preterm births, stillbirths and IUGR babies seen in CVUE are presented in Table 4. Two-thirds of CVUE cases (61/92; 66%) were associated with preterm birth. CVUE occurred at a median gestational age of 35 weeks (31-37) (25th-75th percentile).

Stillbirth was seen in 40% (37/92) (n/N) of CVUE overall. The category of high grade CVUE was significantly associated with stillbirth compared to low grade CVUE (p=0.019). Forty-six percent of cases (42/92) (n/N) were associated with IUGR. The babies of two cases (2/92) (n/N) had adverse neurological outcomes. Two additional babies (2/92) (n/N) with low 5-minute Apgar scores were subsequently lost to follow up. Neonatal death occurred in two cases (2/92).

Discussion

The value of placental pathological examination in the investigation of perinatal morbidity and mortality is well known and includes clarification of the cause of many adverse pregnancy outcomes.[9,16] However, as histological examination is performed postnatally and gives a retrospective account of antenatal events, CVUE might be overlooked as a contributing factor to adverse pregnancy outcomes.[2–5] The importance of placental pathology and its relationship to stillbirth is well described. However, placental lesions associated with stillbirth are extremely varied and poorly defined, and their relation to pathologic processes leading to stillbirth is difficult to assess.[17] The relationship between CVUE and stillbirth remains uncertain. Although CVUE has been reported as an independent risk factor for stillbirth at term, evidence for a demonstrable association between CVUE and stillbirth is scant.[3,18] In a systematic review including 24 case control and cohort studies, a significant link between CVUE and stillbirth could not be reliably established.[3] In the index study stillbirth occurred in a significant minority of CVUE cases, of which nearly two-thirds were associated with high grade CVUE. The category of high grade CVUE showed a statistically significant association with stillbirth compared to low grade CVUE.

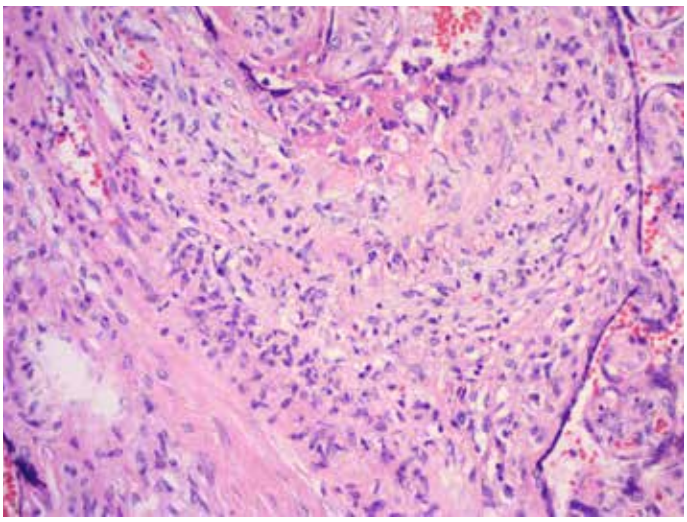
Low birth weight is associated with increased neonatal morbidity and mortality.[8] Chronic villitis is significantly associated with low birth weight and is an independent risk factor for SGA at term.[2,3,8,19,20] In a recent retrospective study investigating the perinatal prognosis of pregnancies complicated by chronic villitis or chronic intervillositis of unknown aetiology, two thirds of 78 CVUE cases (51/78) were associated with IUGR.[10] In the index study IUGR was seen in nearly half of all CVUE cases. There was no significant difference between the categories of low and high grade CVUE for IUGR and preterm births, respectively.

Table 4. Adverse pregnancy outcomes compared with low and high grade villitides. n (%)

	Low grade villitis (n = 47)	High grade villitis (n = 42)	Chi-square: P value
Preterm birth[a] n = 66 (74)	28	30	p=0.39
Stillbirth[b] n = 37 (42)	14 (16)	23 (26)	p=0.019 (*p<0.05)
IUGR[c] n = 42 (47)	22 (25)	20 (22)	p=0.17

[a]Preterm birth designated as birth before 37 completed weeks of gestation.
[b]Stillbirth was defined as foetal death at or after 20 completed weeks of gestation.
[c]Intra-uterine growth restriction was defined as birth weight <10th percentile.

Figure 4. Villitis involving a stem villous. A stem villous with lymphocyte-predominant inflammation (haematoxylin-eosin, original magnification X200)



Infants whose placentas have CVUE are at risk for abnormal neurodevelopmental outcome and death.[21] In a retrospective cohort study of 120 neonates with neonatal encephalopathy, patchy/diffuse chronic villitis was the only single placental pathology shown to significantly predict abnormal long-term outcomes.[22] CVUE with obliteration of stem vessels (i.e. foetal thrombotic vasculopathy) may cause impairment of the fetoplacental circulation, and is associated with adverse outcomes such as neurological impairment, IUGR and IUFD.[6,22-24] Although the placentas of both babies with poor neurological outcomes showed involvement of stem villi (Figure 4), thrombotic occlusion of stem villous vessels was only seen in one case. Neonatal death occurred in two cases, one of which had an additional diagnosis of maternal vascular malperfusion. Conclusions regarding possible associations between CVUE and poor neurological outcomes or neonatal death are limited due to small numbers and the limited follow-up period.

Placental abnormalities with more than one distinct pattern of injury or involving more than one anatomic compartment may act synergistically or sequentially to contribute to adverse pregnancy outcomes. In the index study nearly two-thirds of cases with CVUE had an additional pathological diagnosis that may have contributed to the poor pregnancy outcomes. The higher number of growth restricted infants and stillbirths in this cohort of placentas with CVUE, compared to the literature at large, may in part be attributable to an additional pathologic diagnosis in the majority of cases, or the secondary and tertiary level institution setting with increased rates of high risk deliveries.

Significant associations between CVUE and maternal obesity, multigravidity and ethnicity have been reported in previous studies.[5] Contradictory to the literature, approximately half of all CVUE cases in the index study occurred during the first or second pregnancy, with a decline in the number in subsequent pregnancies. Low and high grade CVUE showed no significant differences in their association with the clinical parameters of gravidity, advanced maternal age, HIV status, hypertension/pre-eclampsia and cigarette smoking.

Although CVUE reportedly accounts for the overwhelming majority of chronic villitides, the number of chronic villitis cases with an infectious cause in this cohort approached 50%, of which congenital syphilis accounted for 90%.[25]

To the authors' knowledge similar studies conducted in low- and middle-income countries (LMIC) are limited. Although larger prospective studies are required to establish causal associations between CVUE, clinical factors and pregnancy outcomes, we believe that the findings in this study add to the current understanding of this poorly understood entity. Ongoing developments may help to identify patients who are at risk for recurrence in subsequent pregnancies.

Study limitations

We acknowledge some limitations in this review. As not all placentas submitted to the Division of Anatomical Pathology meet the criteria for histopathological examination as formulated by the Perinatal Group at Tygerberg Hospital (Table 1), this study is subject to selection bias. In addition, as Tygerberg Hospital is a secondary and tertiary level institution with increased rates of complicated and high risk deliveries, placental pathology may not be representative of that in the general population.

It is possible that the category of CVUE as defined above may include a small number of infectious villitides for which the infectious nature could not be identified by reasonable means.

The lack of a control group limits statistical analysis to a comparison between the association of the grade of villitis and clinical outcomes. This study therefore cannot comment on the overall link between CVUE and clinical outcomes.

In stillbirths the foetal death-to-delivery interval is often uncertain, which may lead to underestimation of weight (due to maceration) and overestimation of gestational age.

Conclusion

The present study, conducted in a LMIC, characterised 92 cases of CVUE (of 173 cases of chronic villitis identified over a 5-year period). High grade CVUE, which accounted for almost half of all CVUE cases, showed a statistically significant association with stillbirth compared to low grade CVUE. The majority of CVUE cases occurred in combination with other placental pathology that may have contributed to adverse pregnancy outcomes. Compared to the literature, chronic villitis with an infectious cause was overrepresented.

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Author contributions

PS and CAW conceived the study, and participated in study design and the interpretation of pathology data. DRH assisted in the acquisition of funding. DM assisted in the collection of clinical data. The corresponding author (VP) performed the literature search, assisted with the analysis of pathology data and drafted the manuscript. All the co-authors discussed the results, and critically revised and approved of the final manuscript.

Conflict of interest statement

The authors declare that they have no competing interests.

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