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Perinatal prognosis of pregnancies complicated by placental chronic villitis or intervillositis of unknown etiology and combined lesions: About a series of 178 cases

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ABSTRACT

Introduction: The objective of this work was to evaluate and compare perinatal outcomes of pregnancies complicated by placental chronic intervillositis (CIUE) or villitis (CVUE) of unknown etiology and combined lesions.
Methods: Retrospective study of all cases of significant CVUE and CIUE occurring during a 12-year period in a university tertiary hospital center. Multiple pregnancies, infectious and medical termination of pregnancies (TOP) without intra-uterine growth restriction (IUGR) were excluded.
Results: 178 placentas were affected (78 cases of CVUE, 24 cases of CIUE and 76 cases of combined lesions involving both villitis and intervillositis) including 12 cases of recurrence. A disorder of fetal growth was found in 73% of cases and we noted 9.5% of cases of abortion. The rate of IUGR appeared to be significantly higher in case of CIUE with a fetal death risk five times higher. These complications seems to be related to more diffuse inflammatory infiltrates ($p < 0.05$). CVUE was associated with a significant morbidity with 42% of severe IUGR and severe alterations of umbilical artery Doppler in nearly one third of cases. Caesarean section was important (54.8%). Sixty-one percent of newborns were hospitalized and 11.4% in neonatal reanimation. In case of combined lesions, fetal outcomes appeared relatively close to those of CVUE. CVUE could recur in more severe forms or as CIUE with an increased risk for the fetus. Clinicoanatomic correlations were noted.
Discussion: Observation of recurrence of CVUE on CIUE or combined lesions and similar phenotypic characteristics of the infiltrates suggest that they could be two different stages of a same disease. CVUE remains a disease to be considered as serious. Association of small lesions of intervillositis does not change the prognosis. The severity of histological lesions and the initial obstetrical accident could be discriminatory to identify patients at risk of serious recurrence. Harmonized classification will be required.
Conclusions: This study confirms the higher morbidity of CIUE compared to CVUE but shows the necessity of monitoring pregnancies following an episode of CVUE, which are still at risk of serious and recurrent complications.

1. Introduction

Chronic villitis and intervillositis of unknown etiology are two inflammatory diseases of placenta accountable for early and late fetal death, most often in a context of intra-uterine growth restriction (IUGR) at high risk of recurrence. Described from 1975 onwards, these lesions are characterized by a mononuclear infiltration of placenta. Chronic villitis of unknown etiology (CVUE) is characterized by a lymphohistiocytic infiltrate at the extremity of the villous stroma whereas chronic intervillositis of unknown etiology (CIUE) is a majority histiocytic's infiltrate in the intervillous

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space. Mechanisms involved in the genesis seem to be close without being able to assert if these are two distinct pathologies or two developmental stages of the same disease. Recently, several authors [1–4] have suggested a more severe prognosis of CIUE that, although infrequent, would be associated with earlier complications and a high rate of fetal death, resulting in a progressive disinterest for CVUE. However, no study has compared specific morbidity and mortality of the two diseases. Similarly, lesions involving both villitis and intervillositis have an uncertain prognosis and still considered as CIUE.

This study presents all cases of CVUE and CIUE diagnosed over 12 years in a university tertiary hospital center and compares perinatal outcomes of related pregnancies.

2. Materials and methods

This retrospective study was performed at a university hospital center carrying more than 3500 deliveries per year. In this hospital, placentas are analyzed in the main following situations: IUGR, small for gestational age (SGA), unexplained bleeding and unexplained poor adaptation at birth. Patients were identified from the department of histopathology database. All products of abortion and placentas of complicated pregnancies were submitted for pathologic examination in this center. For this study, eligible patients are the ones who have placenta or products after spontaneous first trimester miscarriage with lesions of CVUE or CIUE, between January 1998 and July 2010.

Placentas and products of early abortion were fixed in formalin within 24–48 h. Multiple samples were then set in paraffin blocks 5 μm thick for haematoxylin-eosin-saffron (HES) staining. Each sample was read by one of the two pathologists specialized in fetal pathology with agreement between the two in case of doubt. CVUE were defined by the presence of a mononuclear lymphohistiocytic's infiltrate in villous chorion, without reaching the intervillous space. CIUE was defined by the presence of a major mononuclear histiocytic's infiltrate in the intervillous space with or without fibrin deposits. When the infiltrate was localized both in the villi and the intervillous space, lesions were named "combined lesions". Minimal lesions were not specified by pathologist. Due to the absence of international agreement, a semi-quantitative grading as Marchaudon and al [1] was used, where the extent of cell infiltration is measured. The infiltrate was considered diffuse when there were clusters of cells filling the entire villous or intervillous space uniformly and massively at a magnification 100 and was multifocal when the clusters were distributed heterogeneously, varying from one microscopic field to another. The intensity of infiltrate was considered high when the clusters of cells completely filled the villous or intervillous space, moderate when the clusters were less voluminous and low when they contained only a few cells. Characteristics of the infiltrate were recorded on the anatomical pathology report by a third reporter. The biometrics and placental weight were measured using curves of Philippe [5] and Nessmann [6].

Chronic villitis and intervillositis with infectious etiology were excluded as well as twin pregnancies or damage discovered after termination of pregnancy (TOP) for other reasons than severe and early growth restriction.

All maternal and obstetric data were collected from archived obstetric records.

The curves of the French College of Fetal Ultrasound [7] were used as reference in analysis of fetal biometrics. IUGR was defined by a growth failure with biometrics below the 10th percentile and SGA at birth by a weight below the sex-adjusted 3rd percentile on AUDIPOG curves [8,9]. Severity of IUGR was classified artificially into three groups: below the third percentile, 3rd–10th percentile and 10th percentile. Umbilical Doppler alteration was considered severe in case of no diastolic or reverse flow.

Early or late interruption of pregnancy was defined as a pregnancy stopped before 14 weeks of gestation or between 14 and 22 weeks; fetal death regrouped all pregnancies stopped after 22 weeks. Pregnancy-induced hypertension was defined as hypertension $\geq$140/90 mmHg and preeclampsia associated hypertension with proteinuria $\geq$300 mg/liter.

The data were collected by a single investigator. Statistical analysis was performed using the 2 x Epidata analysis. Comparisons between qualitative data used the Chi-square test or Fisher's exact test, when the number of individuals was low. Comparison of quantitative variables appealed to nonparametric Kruskal Wallis test or t (ANOVA). The significance level used was $p < 0.05$. When the Chi2 was not calculable because of too low numbers, the results were recorded as invalid (NS).

3. Results

During these 12 years, 4100 placentas with complicated pregnancies and 2800 products of early abortions were analyzed in this center for approximately 42 000 deliveries.

About 281 placentas presented lesions of villitis or intervillositis. No lesions were found on products of early abortion. After exclusion of multiple pregnancies, infectious and TOP without IUGR, 178 placentas were considered eligible. The overall prevalence of lesions was estimated as 4.3% of placentas analyzed. Among these inflammatory lesions, 78 cases of CVUE were counted (1.9% of placentas analyzed), 24 cases of CIUE (0.6% of analyzed placentas) and 76 cases of combined lesions (1.8% of placentas analyzed). There were 166 single episodes and 12 cases of recurrence. Maternal characteristics were comparable in all groups.

Overall, CVUE and CIUE have been associated with 9.5% of antenatal fetal loss in any term (Table 1). Among the pregnancies over 22 weeks, disorder of fetal growth was observed in 73% of cases (Table 2) and was severe in about half of cases (Table 3). The rate of caesarean section was high (54.7%) compared to the rate of 20% in this center, as neonatal morbidity with 55.2% of newborns hospitalized in a neonatal unit care (Table 4).

Obstetric complications were analyzed according to the histological specific type. No difference was found with the association of preeclampsia or gestational hypertension (Table 2).

CIUE was associated with severe morbidity: the rate of antenatal fetal loss was five times higher compared to CVUE (29.2% vs 6.4%) with an earlier risk since only CIUE was associated with three cases of late miscarriages (Table 1). The rate of IUGR appeared also significantly higher (81% vs 66.2%, $p = 0.006$), with IUGR more severe (76.5% vs 42%) and a term of occurrence 5 weeks earlier on average ($p = 0.003$) (Tables 2 and 3). In case of live births, the average age of birth (2 weeks before ($p < 0.005$)) and the weight of newborn ($p = 0.003$) appeared significantly lower compared to CVUE. The caesarean section rate was significantly higher (82.4% vs 54.8%, $p = 0.03$) as well as the rate of indicated preterm birth (64.7% vs 43.5%, $p = 0.01$).

In case of CVUE, it was found IUGR in two third of cases with severe alterations of Doppler for third of cases. In 10.3% of cases, SGA was late and undiagnosed in utero (Table 2). In this group, the rate of vaginal release appeared higher, but caesarean section was nevertheless important (54.8%). Sixty-one percent of newborns were hospitalized and 11.4% in neonatal reanimation unit.

In case of combined lesions, data on obstetric complications and fetal outcomes appear relatively close to those of CVUE (Tables 1–4).

Analysis on placental data showed severe SGA in 37.6% of cases. There was no difference for placental biometrics according to the