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# Macroscopic and histological characteristics of retained placenta: A prospectively collected case-control study

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ABSTRACT

*Introduction:* Retained placenta is a potentially fatal obstetric disorder due to postpartum hemorrhage, its pathophysiology is however unknown. We aimed to assess if retained placenta was associated with increased macroscopic and histological signs of placental maternal underperfusion, a pattern otherwise seen in preeclampsia and other disorders of defective placentation.
*Methods:* This was a case-control study of retained (n = 49) and non-retained (n = 47) placentas, collected from full-term singleton and otherwise healthy pregnancies, carried out at a tertiary level obstetric department. Macroscopic and histological analysis was performed. Signs of maternal placental underperfusion and signs of placental inflammation, fetal vascular thrombo-occlusive disease and increased placental attachment were recorded in a primary and secondary analysis respectively. Variables were compared groupwise using unconditional logistic regression or comparison of median or mean values.
*Results:* Compared to non-retained placentas retained placentas had a significantly smaller surface area (p = 0.05), were more oblong in shape (OR 5.24 95% CI:1.34–20.21) and showed overall more signs of maternal underperfusion (OR 2.52 95% CI: 1.07–5.87). There was no significant difference in signs of placental inflammation, fetal vascular thrombo-occlusive disease or placenta accreta but basal plate myometrial fibers were more common among retained placentas.
*Conclusion:* In regard to shape, surface area and histological signs of maternal placental underperfusion, retained placentas showed a histological pattern similar to that seen in preeclamptic placentas.


## 1. Introduction

Retained placenta is one of the main causes of severe postpartum hemorrhage and maternal death due to postpartum hemorrhage [1,2]. Despite this the etiology as well as the histological characteristics of the disorder are largely unknown.

Retained placenta arises as a complication to approximately 3% of all deliveries [3]. It is commonly defined as a placenta that has not detached within 30 min of delivery; manual removal is usually required either to achieve placental separation or in response to hemorrhage [4]. The disorder is sometimes assumed to be a milder form of placenta accreta, incidence 0.04%, however the relationship is uncertain [5]. Retained placenta does not by definition present with defects in the basal decidua and does not share all of the same risk factors as placenta accreta [5,6].

Previous studies have shown an epidemiological association between retained placenta and preeclampsia, preterm birth, fetal growth restriction and a history of recurrent miscarriages [7–9], disorders associated with an initial defective placentation and increased placental oxidative stress [10]. There is however no known pathophysiological association between retained placenta and these disorders.

Defective placentation in preeclampsia and fetal growth restriction occurs as a results of incomplete spiral artery remodelling with persistence of smooth muscle in placental spiral arteries leading to perfusion reperfusion injury in the placental tissue and oxidative stress [11]. Placentas from preeclamptic and growth restricted pregnancies are characterized by atherosis and increased histological signs of maternal underperfusion such as placental infarction, increased syncytial knotting and terminal villous fibrosis [12,13]. Although these changes are more prominent in early onset preeclampsia and fetal growth restriction, as well as preeclampsia

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concurrent with fetal growth restriction [14], they are increased also in late-onset preeclampsia and fetal growth restriction, when compared to placentas from normal pregnancies [15,16]. Studies have suggested that most disorders considered to be part of the defective placentation spectrum present with an increased degree of atherosis in the placenta [17]. Preeclampsia is also associated with an excessive systemic inflammatory response evident in maternal serum and in placental tissue but acute histological inflammation does not seem to be increased [15,18].

Macroscopic and histological features of retained placenta have to our knowledge not been prospectively studied and its relationship to other disorders of placentation remains unknown. We aimed to assess if histological signs of maternal underperfusion were increased in retained compared to non-retained placentas in otherwise normal full-term pregnancies, and if there were macroscopic traits to retained placenta consistent with placental underperfusion.

## 2. Methods

### 2.1. Sample collection and histological analysis

We performed a case-control study data based on placentas collected prospectively between February 2013 and September 2014 at a tertiary level delivery ward in Stockholm, Sweden. The total study group consisted of 50 retained placentas and 50 spontaneously released placentas. All included placentas came from live full-term singleton births with no clinical indications of preeclampsia or diabetes (both defined according to the 10th version of International Classification of Diseases, ICD-10) or small-for-gestational-age birth (defined as birthweight two standard deviations or more below the mean weight for gestational age according to the Swedish sex-specific fetal birth weight curve) [19]. Within a few days of each retained placenta being included in the study, a randomly selected on-going delivery was selected from the in-patient list and recruited to the study if the placenta was spontaneously released. One retained placenta was excluded after inclusion due to non-recognized diabetes in the mother and three control placentas never reached the pathological lab leaving a final study group of 49 retained placentas and 47 controls.

Placental examination was performed as previously described [20]. Macroscopic examination included evaluation of the form of the placenta (including presence of accessory lobes), the fetal membranes, the fetal and maternal surfaces, the presence of focal changes in the parenchyma and insertion and coiling of the umbilical cord. Placentas were weighed after formalin fixation and removal of the fetal membranes and the umbilical cord and categorized as under the10th percentile, between the 10th and 90th percentile, or above the 90th percentile of weight for gestational age according to a reference curve [21]. Fetal to placental weight ratio was estimated. Full-thickness placental biopsies were taken from three different macroscopically normal placental sites as well as sites with focal macroscopic changes. Fresh and older infarctions were included. Histological sections were taken from at least one of the macroscopically suspected infarcted areas. Villous necrosis seen at the periphery of older intervillous thrombi as well as in areas of extensive intervillous fibrin deposition was not assessed as infarction. A complete 1 cm thick full-lumen sample of the umbilical cord was collected. The samples were fixed in buffered formalin, paraffin embedded, cut and stained for a detailed protocol-led microscopic analysis.

The presence of the following histological variables was assessed: villous maturation, decidual arteriolopathy, infarction, intervillous and fetal thrombosis, chorangiosis, septal cysts, fibrotic villi, syncytial knots and/or villous agglutination, grouped multinucleated trophoblastic cells, chronic villitis, chorioamnionitis, vasculitis, funisitis, basal plate myometrial fibers (BPMF), signs of placental abruption and placenta accreta.

### 2.2. Outcome

Retained placenta was defined as the identification of an adherent plane between the placenta and the uterine wall during manual removal of the placenta, thus excluding cases where the placenta was trapped behind a contracted cervix.

### 2.3. Main exposures

Artheriolopathy, placental infarcts, giant trophoblastic multinucleated giant cells, syncytical knots/villous agglutination, chorangiosis, septal cysts and fibrotic villi were considered histological features of maternal underperfusion. Decidual arteriolopathy was defined as fibrinoid necrosis of the spiral artery wall, often with dilation of the vessels, presence of acute atherosis and lumen thrombosis; placental infarction as ischemic necrosis of the villi. The proportion of infarcted placental tissue was calculated by dividing the total volume of the infarcts by the total volume of the placenta. Chorangiosis was recorded in the presence of vascular hyperplasia in the terminal chorionic villi and defined according to Altshuler's criteria [22]. Grouped multinucleated trophoblastic cells was defined as three or more clustered trophoblasts in the decidua each with three or more nuclei [23]; syncytial knots as >10 aggregated syncytial nuclei at the surface of the terminal villi often with collapse of the villous space (villous agglutination) [24,25].

### 2.4. Secondary exposures

Acute chorionitis or chorioamnionitis and acute vasculitis or funisitis were considered lesions consistent with maternal or fetal placental inflammatory response respectively. Acute inflammation was recorded in the presence of neutrophils in the chorion or subchorion (subchorionitis/chorionitis), with expansion into the chorioamniotic mesoderm and/or amnion (chorioamnionitis). Umbilical vasculitis was defined as the presence of neutrophils in the wall of the umbilical cord. Funisitis was recorded if the inflammation extended into Wharton's jelly. Chronic villitis was defined as the presence of lymphocytes with or without histiocytes in the stroma of placental villi.

Villous maturation was evaluated in relation to gestational week. The size and configuration of the dominant villous component was assessed, including the layer of trophoblasts and the number and morphology of blood vessels. Areas adjacent to infarction were not included in the assessment of maturation. The presence of intervillous thrombosis was recorded, including fresh and older lesions. Smaller areas of subchorial thrombosis commonly found in placentas were not recorded as intervillous thrombosis. Fetal thrombosis was defined as thrombosis in the vessels of the umbilical cord, chorionic plate or stem villi. Though placental abruption is a clinical diagnosis, the presence of a retroplacental hematoma was recorded as suggestive of the disorder. BPMF were recorded in the presence of smooth muscle cells at the maternal floor with intervening decidua. Placenta accreta was defined as a focal absence of intervening decidua between the chorionic plate and the myometrium.

All histological analysis was performed at Karolinska University Hospital, Department of Perinatal Pathology by an experienced perinatal pathologist (NP). The pathologist was blinded in regard to the outcome group for all microscopic analysis. Written consent was ascertained from each study participant. The study was approved by the Ethics Committee at Karolinska Institutet, Sweden (2012/15-31/2).