



## **Factors associated with poor fetal outcome in placental abruption**

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### **► To cite this version:**

Claire de Moreuil, Jacob Hannigsberg, Juliette Chauvet, Annabelle Remoue, Christophe Tremouilhac, et al.. Factors associated with poor fetal outcome in placental abruption. *Pregnancy Hypertension*, 2021, 23, pp.59 - 65. <10.1016/j.preghy.2020.11.004>. <hal-03493046>

**HAL Id: hal-03493046**

**<https://hal.science/hal-03493046v1>**

Submitted on 1 Apr 2022

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## **Title page:**

### **Type of article: Full length article**

### **Title: Factors associated with poor fetal outcome in placental abruption**

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## **Abstract:**

**Objectives:** We aimed at describing placental abruption in our county and at evaluating factors associated with poor fetal outcome.

**Study design:** In this case-control study, women with placental abruption were identified from two databases of Brest University Hospital between January 2013 and December 2018.

**Main outcome measures:** Placental histological findings, course of pregnancies, maternal and fetal characteristics were described and compared between cases (placental abruption with stillbirth or neonatal death) and controls.

**Results:** We identified 135 placental abruption, of whom 24.4% were complicated with stillbirth and 6.5% with neonatal death. Forty percent of women were smokers and 14.1% had a history of vasculoplacental disorder. Pregnancies were complicated with 42.2% of pre-eclampsia and 43% of intrauterine growth restriction. Cases were associated with more autoimmune diseases in mother (20.0% versus 3.2%,  $P = 0.003$ ), more aspirin or heparin use during pregnancy (20.0% versus 6.3%,  $P = 0.03$ ), less pre-eclampsia (25.0% versus 49.5%,  $P = 0.01$ ) and more deliveries  $\leq 34$  weeks of gestation (80.0% versus 43.2%,  $P = 0.0001$ ) than controls. Placentas from cases showed more placental indentation  $\geq 30\%$  (42.5% versus 5.3%,  $P < 0.0001$ ) and less histological chronic inflammation, especially less chronic chorioamniotitis (2.5% versus 24.2%,  $P = 0.002$ ) than controls. In multivariate analysis, factors negatively associated with poor fetal outcome were placental histological chronic inflammation ( $P = 0.01$ ) and macroscopic infarcts ( $P = 0.01$ ).

**Conclusions:** Poor fetal outcome is negatively associated with certain placental histological chronic lesions, but not with pre-eclampsia, what suggests various pathophysiological processes among placental abruption.

**Keywords:** placenta; abruption; inflammation; chorioamniotitis; pre-eclampsia; stillbirth.

**Abbreviations:**

Body Mass Index = BMI

Confidence interval = CI

Disseminated intravascular coagulation = DIVC

Feature elimination algorithm = RFE

Fetal vascular malperfusion = FVM

Hemolysis, elevated liver enzymes and low platelet = HELLP

Hematoxylin, Eosin and Saffron = HES

Human Leukocyte Antigen = HLA

Interquartile range = IQR

Intrauterine growth restriction = IUGR

Low molecular-weight heparin = LMWH

Maternal vascular malperfusion = MVM

Medical Registry Department = MRD

Odd Ratio = OR

Weeks of gestation = WG

## **Main text :**

### **Introduction :**

Placental abruption is a feared obstetrical complication, observed in 0.4 to 1% of pregnancies, and defined as a detachment of the placenta before delivery [1,2]. Its clinical presentation can be very sudden, endangering both mother and fetus through maternal hemorrhage and fetal hypoxia. It represents a therapeutic emergency for obstetricians, the main objective being to extract the fetus as soon as possible and to manage maternal hemorrhage and resulting coagulation abnormalities [3,4]. However, main fetal mortality occurs in utero, sometimes without any maternal symptom, what raises the question of its avoidability [5].

Risk factors to develop placental abruption have been well studied. They are in one hand related to maternal baseline characteristics (tobacco or cocaine use, thrombophilia, previous placental abruption...), and in another hand influenced by the course of the pregnancy such as onset of pre-eclampsia, premature rupture of membranes or infectious chorioamnionitis [5-7].

Despite the suddenness of its clinical presentation, more and more data in the literature suggest an underlying silent and chronic process starting weeks or months before the clinical event [8,9]. Along with this, a prospective American cohort study (the Collaborative Perinatal Project) on 46364 deliveries described some placental chronic histological lesions such as chronic deciduitis and placental infarcts as risk factors for placental abruption [9].

We report here the results from a retrospective observational study on placental abruption in our county. We aimed to describe clinical and histological features of placental abruption and to evaluate factors associated with poor fetal outcome through a case-control study.

### **Methods:**

#### **Selection of participants:**

Women with placental abruption were identified between January 2013 and December 2018 from two databases available in Brest University Hospital.

The first database was the Medical Registry Database (MRD) of Brest University maternity ward and of four other maternity wards of our county. Women were identified by using the term "placental abruption". The five maternity wards were unselected: they were public as

well as private maternity wards and ranged from level 1 to level 3 according to the level of care available for the newborns.

The second database was the specific database (ADICAP system) of the Pathology department files that records all histological diagnoses. Placentas were identified by searching for the term “retroplacental hemorrhage”. Every potential placental abruption was reviewed by an experienced obstetrician (C.T.) in order to confirm the accuracy of the diagnosis. Placental abruption was clinically defined and was not only diagnosed by histological examination [10]. In case of discordant results (placental abruption clinically diagnosed but not confirmed by histological examination), the clinical definition was retained.

We excluded duplicates, medical termination of pregnancy, marginal abruption, placenta previa, placental abruption without histological examination of the placenta, histological placental abruption without compatible clinical signs and placental abruption from a maternity outside our county.

“Cases” were defined as placental abruption with poor fetal outcome (stillbirth or neonatal death). “Controls” were defined as placental abruption with good fetal outcome (a live newborn still alive at day 28).

Women identified with a placental abruption were sent an information letter explaining the study and its purpose. We excluded women who expressed their opposition to participate to the study.

The study was approved by the institutional review board of Brest University Hospital.

### **Clinical parameters:**

Methods of clinical parameters logging are described in details elsewhere [11].

The following data were recorded from medical files: baseline maternal characteristics including preconceptional Body Mass Index (BMI), tobacco and drug use during pregnancy, medical history (chronic hypertension, chronic nephropathy, diabetes, cardiovascular disease, autoimmune disease, inflammatory rheumatic disease, previous venous thromboembolism), obstetrical history, especially previous vasculoplacental disorder (defined by one of the following conditions: pre-eclampsia, intrauterine growth restriction (IUGR), placental abruption), age at delivery. The following pregnancy characteristics were also collected: method of conception, medication during pregnancy (in particular aspirin and low molecular-weight heparin (LMWH)), gestational diabetes, premature rupture of membrane, pre-

eclampsia (according to the American College of Obstetricians and Gynecologists' definition published in 2013), term at pre-eclampsia diagnosis, term at delivery and method of delivery, postpartum complications including postpartum hemorrhage (defined by a blood loss > 500 ml, whatever the mode of delivery), disseminated intravascular coagulation (DICC), thromboembolic event after delivery and before hospital discharge, intensive care admission in postpartum and length of stay [12,13].

The following fetal characteristics were recorded in order to classify placental abruption in the "case" group or in the "control" group: presence and term at IUGR diagnosis, stillbirth, birth weight and sex of the newborn. IUGR was defined according to the 2013 French College of Obstetricians and Gynecologists guidelines by an estimated fetal weight below the 10<sup>th</sup> percentile using locally-accepted curve (AUDIPOG) associated with signs of fetal growth pathological restriction [14]. Neonatal death was defined according to the World Health Organization as a death among live births during the first 28 completed days of life [15].

#### **Placental parameters:**

Histopathological examinations of the placentas were performed by two senior perinatal pathologists at Brest University Hospital.

Placentas were fixed in 4% buffered formalin. Standard sampling of three blocks in the central area was performed and slides were Hematoxylin, Eosin and Saffron (HES) stained.

Recorded macroscopic findings corresponded to the following items: placenta weight, fetoplacental weight ratio, retroplacental hemorrhage, abnormal membrane insertion (only circumvallation), abnormal umbilical cord (velamentous implantation, thin umbilical cord with < 0.8 cm in diameter, presence of a knot), presence and number of histologically confirmed macroscopic placental infarcts, intervillous thrombi and subchorial hematoma affecting  $\geq$  one third of the placental surface. The retroplacental hemorrhage was considered as chronic in the presence of at least one of the three following features: indentation of the placental parenchyma, adherence and organization of the clot, presence of an infarct on the overlying placenta. Percentage of the placenta affected by the indentation was recorded when present [16].

Recorded microscopic lesions corresponded to the following items according to Amsterdam consensus: maternal vascular malperfusion (MVM) lesions such as microscopic infarcts, decidual arteriopathy, abnormal villous maturation (hypermaturation villi or villous agglutination), presence of fetal vascular malperfusion (FVM) signs such as obliterative fetal

vasculopathy or avascular villi, chorangiosis and erythroblastosis and excessive fibrin deposition. Microscopic infarcts were defined as infarcts that were identified histologically but were too small to be seen macroscopically.

Placental chronic inflammation, defined as one of the following features, was systematically sought: chronic villitis of unknown etiology, chronic intervillitis of unknown etiology, chronic chorioamnionitis, and chronic deciduitis. Acute inflammation, such as acute villitis, acute chorioamnionitis or funisitis, was also recorded.

Chronic villitis was classified in high or low grade. High grade chronic villitis was defined by the presence of inflammation affecting more than 10 contiguous villi in any focus, with more than one focus required for diagnosis [17]. VUE was also defined according to the location of the inflammatory infiltrate: proximal stem villi and sometimes chorionic plate (*i.e.* subchorial), distal villi (*i.e.* parenchymatous), anchoring villi embedded in the basal plate (*i.e.* basal) [16]. Criteria used for CIUE diagnosis were the same as developed by Bos *et al* [18].

Chronic chorioamnionitis was defined according to Kim CJ *et al* and chronic deciduitis was defined according to Khong TY *et al* [19,20].

Immunohistochemistry was systematically used to confirm the diagnosis of chronic inflammation in placenta, as well as to localize and characterize inflammatory cells.

### **Statistical analysis:**

Quantitative variables were summarized using median and interquartile range (IQR). Categorical variables were summarized as frequency (%) of categories.

Differences between cases and controls for categorical variables were analyzed by the Chi square test (or Fisher's exact test if the number of individuals was < 5). For continuous variables, differences between cases and controls were analyzed by nonparametric tests: the Mann and Whitney U test for comparison between two groups. The significance level used was  $P < 0.05$ .

A multivariable logistic regression analysis was also performed to predict poor fetal outcome (*ie* stillbirth or neonatal death) from a set of placental histological parameters and pregnancy parameters. These parameters were selected to perform a logistic regression using the recursive feature elimination algorithm (RFE). The log likelihood  $R^2$  p-value (LLR p-value) of the model was 0.018, indicating a good fit of the data. The strength of the association between these parameters and poor fetal outcome was expressed as odd ratios (OR) with 95%

confidence intervals (95% CIs). Variables in the model were considered significantly contributive when their associated p-value were < 0.05.

All statistical analyses were performed with GraphPad Prism V5 and Python (3.6).

## **Results:**

### **General characteristics of the population:**

Between January 2013 and December 2018, the selection process allowed us to identify 135 pregnancies complicated by placental abruption (**figure 1**). One woman had two pregnancies with placental abruption.

Clinical characteristics of the 134 women and of the 135 pregnancies are detailed in **Table 1**.

Tobacco use during pregnancy was frequent (40.0% of the pregnant women).

10.4% of the pregnant women received low dose aspirin or prophylactic LMWH for previous vasculoplacental disorder or previous thromboembolic event.

Vasculoplacental disorders were frequent (42.2% pre-eclampsia, 43.0% IUGR), as well as stillbirth (23.6%) and hemorrhagic disorders (24.4% postpartum hemorrhage, 10.9% DVC). Median gestational age at delivery was 34 weeks of gestation (WG). There were 6.5% of neonatal deaths, attributable in majority to extreme prematurity.

The description of histological features of the 135 corresponding placentas is presented in **Table 2**.

Placentas from women with placental abruption showed 25.2% prevalence of chronic inflammation (17.8% chronic chorioamnionitis, 7.4% chronic villitis or chronic intervillitis, 3.7% chronic deciduitis). Chronic inflammatory lesions overlapped in the same placenta in five out of 34 placentas. Among the 10 chronic villitis, eight were low grade villitis and two were high grade villitis. The **figure 2** illustrates a placenta showing features of chronic chorioamniotitis.

Retroplacental hemorrhage was diagnosed on histological analysis in 77.0% of placental abruption. 58.5% of these histologically confirmed placental abruption had chronic features such as presence of an indentation, of an adherent clot or of an infarct on the overlying placenta. The **figure 3** illustrates one of these chronic retroplacental hemorrhages.

MVM lesions were more frequent than FVM lesions (73.3% versus 14.1%). Among MVM lesions, macroscopic infarct was the most frequent feature.

### **Characteristics of placental abruption according to fetal outcome:**

To assess the characteristics of placental abruption according to fetal outcome, we first compared cases with poor fetal outcome, *ie* with stillbirth or neonatal death, to controls.

Baseline maternal characteristics were similar in the two groups, except for autoimmune diseases which were more common in cases than in controls (20.0% versus 3.2%,  $P = 0.003$ ) (**Table 1**). In the case group, two women had an antiphospholipid syndrome, four had a Hashimoto's thyroiditis, one had an immune thrombocytopenia and one had a systemic sarcoidosis.

Women received more frequently low dose aspirin or prophylactic LMWH during pregnancy in the case group than in the control group (20.0% versus 6.3%,  $P = 0.03$ ). Four of the 14 women treated with aspirin or LMWH during pregnancy had an autoimmune disease (two antiphospholipid syndromes, one Hashimoto's thyroiditis and one immune thrombocytopenia) and all of them experienced stillbirth.

Pre-eclampsia and gestational diabetes were less frequent in the case group (25.0% versus 49.5%,  $P = 0.01$  and 0% versus 18.9%,  $P = 0.002$ ), whereas deliveries  $\leq 34$  weeks of gestation, newborns  $< 1000$  grams and DVC were more common in this group, compared to the control group (80.0% versus 43.2%,  $P = 0.0001$ ; 45.0 versus 8.4%,  $P < 0.0001$ , and 30.0% versus 2.1%,  $P < 0.0001$ , respectively).

Placentas from cases showed more placental indentation  $\geq 30\%$  (42.5% versus 5.3%,  $P < 0.0001$ ) and less histological chronic inflammation (7.5% versus 32.6%,  $P = 0.002$ ), especially less chronic chorioamnionitis (2.5% versus 24.2%,  $P = 0.002$ ) than controls (**Table 2**).

In multivariate analysis, factors negatively associated with poor fetal outcome were placental histological chronic inflammation ( $Z = -2.40$ , OR = 0.07 (CI95% = 0.01-0.61),  $P = 0.01$ ) and placental macroscopic infarcts ( $Z = -2.49$ , OR = 0.04 (CI95% = 0.00-0.49),  $P = 0.01$ ). Tobacco use in mother did not reach significance ( $Z = -1.88$ , OR = 0.09 (CI95% = 0.01-1.10),  $P = 0.06$ ) (**Table 3**).

## **Discussion:**

In this retrospective multicenter study, we first aimed to describe placental abruption registered in our county. Vasculoplacental disorders were frequent in our study. They are known to be associated with placental abruption and are mostly the consequence of an impaired implantation of the placenta [21,22]. Furthermore, our study confirmed that chronic inflammation is frequent in placentas of placental abruption, as previously described by Ananth *et al* [9].

Our aim was also to evaluate factors associated with poor fetal outcome in placental abruption. Indeed, risk factors for placental abruption are well described in the literature but clinical and placental histological parameters associated with poor fetal outcome among placental abruption have been less extensively investigated.

Our study showed first that, in the context of placental abruption, cases with poor fetal outcome were associated with more autoimmune diseases in mother and more aspirin or heparin use during pregnancy than controls. However, these two maternal characteristics were entangled. Indeed, all the women who had an autoimmune disease and were treated with aspirin or heparin during pregnancy experienced stillbirth. Antiphospholipid syndrome is known to be responsible for pregnancy morbidity, especially severe ones, such as early placental abruption or stillbirth [23]. History of pregnancy morbidity and/or thrombosis, association with systemic lupus erythematosus and/or autoimmune diseases, and triple antiphospholipid antibodies positivity seem to be predictive of poor pregnancy outcome [24]. Similarly, hypothyroidism is a known risk factor for placental abruption, but it is uncertain if levothyroxine therapy prevents or not this complication and there is no data about severity of placental abruption and hypothyroidism during pregnancy [25-28].

Then, in our study, placental abruption cases with poor fetal outcome showed less pre-eclampsia and more deliveries  $\leq 34$  WG than controls. One retrospective study on placental abruption in French Guiana noted that stillbirth was associated with absence of pregnancy monitoring and with preterm delivery [29]. Another Chinese study found that placental abruption associated with pre-eclampsia and/or IUGR had a poorer prognosis of newborns [30], what is not concordant with our findings.

Our study also pointed out that placentas from cases with poor fetal outcome laid out more placental indentation  $\geq 30\%$  and less histological chronic inflammation, especially less chronic chorioamnionitis than controls. Several studies already described a placental

disruption surface  $\geq 45$  or 50% as a risk factor for stillbirth, which is concordant with our findings [3,31-33]. In a recent retrospective study, histologic chorioamnionitis was independently associated with adverse neonatal outcome in placental abruption [34]. However, the authors did not distinguish chronic and acute chorioamnionitis. Yet, these two histological entities do not share the same pathophysiology. Acute chorioamnionitis is characterized by a neutrophilic infiltrate and is mostly caused by an acute ascending infection [35], whereas chronic chorioamnionitis is composed of macrophages and T cytotoxic lymphocytes and is thought to be a manifestation of a maternal antifetal rejection setting throughout pregnancy [36].

Our findings illustrate that pregnancies complicated with placental abruption are heterogeneous and may result from various pathophysiological processes. Indeed, placental abruption with a livebirth seems associated with chronic clinical and placental histological features. As chronic placental inflammation can be considered as a manifestation of a maternal antifetal rejection, which is a maternal systemic inflammatory response against the fetus, these types of placental abruption could be clinical manifestations of this rejection [37]. Lowered Human Leukocyte Antigen (HLA)-G levels have been described in women affected by placental abruption, which is concordant with a defect in fetal tolerance processes leading to excessive inflammation and then to secondary ischemic placental disease, such as placental abruption [22,38]. Future research may be conducted to better characterize the maternal antifetal rejection in the context of placental abruption, especially by the mean of maternal inflammatory biomarkers throughout the pregnancy.

On the contrary, cases with poor fetal outcome seem to result from an acute and unpredictable process, *i.e* the rupture of a uterine artery. Women with autoimmune diseases seem to be more at risk of placental abruption associated with poor fetal outcome.

Our study has some strengths. Every placental abruption was validated by both an obstetrician and an anatomopathologist, what makes the diagnosis of placental abruption robust. Besides, we analyzed in detail placental histological features of placental abruption, macroscopic as well as microscopic lesions.

Our study has also some limitations. It is a small retrospective study. There is also a bias related to selection of placental abruption with an available histological analysis of the placenta. Therefore, we may have selected the most severe placental abruption.

## **Conclusions :**

Placental histological examination is a mandatory complementary tool to assert the diagnosis of placental abruption and to determine its etiology. Placental chronic inflammation, as a manifestation of a maternal antifetal rejection, is frequent in placental abruption and is negatively associated with poor fetal outcome. On the contrary, pre-eclampsia is not associated with poor fetal outcome. This study suggests then various pathophysiological processes among placental abruption.

## **Acknowledgements:**

We thank the teams of the five maternities of the county for their participation in this study: midwives, obstetricians and secretaries. We thank the archivists of Brest University Hospital. We thank the patients included in the study. We thank the technical staff of Brest Pathology department and have a thought for Dr Francoise Ledé. We thank Dr Marie-Pierre Moineau and the technical staff of Brest Biochemistry department. Last, but not least, we thank Nathan Foulquier for his help with statistical analysis.

## **Authorship confirmation statement:**

All the authors have contributed significantly to this manuscript and have approved its final version.

Claire de Moreuil designed the work, collected data, analyzed and interpreted them and wrote the manuscript.

Jacob Hannigsberg, Juliette Chauvet, Philippe Merviel, Charles Bellot, Brigitte Pan Petesch and Emmanuelle Le Moigne contributed to design the work and revised the manuscript.

Annabelle Remoue performed histological analyses and revised the manuscript.

Christophe Tremouilhac reviewed all pregnancies complicated with placental abruption in order to confirm or not the diagnosis and revised the manuscript.

Karine Lacut contributed to design the work, to analyze and to interpret data and revised the manuscript.

Pascale Marcorelles performed histological analyses, contributed to design the work, to analyze and to interpret data and revised the manuscript.

**Funding statement :**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Tables:

**Table 1.** Mothers and pregnancies characteristics of placental abruption according to fetal outcome

	All placental abruption n = 135	Placental abruption without stillbirth or neonatal death n = 95	Placental abruption with stillbirth or neonatal death n = 40	p
<b>Baseline maternal characteristics</b>				
Nulliparous (%)	68 (50.4)	50 (52.6)	18 (45.0)	0.5
≥ 2 miscarriage (%)	11 (8.1)	7 (7.4)	4 (10.0)	0.7
Previous vasculoplacental disorder (%)	19 (14.1)	13 (13.7)	6 (15.0)	0.8
Assisted conception (%)	11 (8.1)	6 (6.3)	5 (12.5)	0.3
Median mother's prepregnancy BMI (kg/m <sup>2</sup> )	23 (20-27)			
Obesity (BMI ≥ 30) (%)	21 (15.6)	15 (15.8)	6 (15.0)	1
Overweight ( 25 ≤ BMI < 30) (%)	28 (20.7)	20 (21.1)	8 (20.0)	1
Underweight (BMI ≤18) (%)	13 (9.6)	10 (10.5)	3 (7.5)	0.8
Median age at delivery (years)	30 (27-35)			
Age at delivery ≥ 35 (%)	29 (21.5)	19 (20.0)	10 (25.0)	0.5
Tobacco use (%)	54 (40.0)	41 (43.2)	13 (32.5)	0.3
Drug use (%)	6 (4.4)	4 (4.2)	2 (5.0)	1
Chronic hypertension (%)	4 (3.0)	1 (1.1)	3 (7.5)	0.08
Chronic nephropathy (%)	7 (5.2)	4 (4.2)	3 (7.5)	0.4
Diabetes (%)	2 (1.5)	2 (2.1)	0	1
<b>Autoimmune disease or inflammatory rheumatic disease (%)</b>	<b>11 (8.1)</b>	<b>3 (3.2)</b>	<b>8 (20.0)</b>	<b>0.003</b>
Previous venous thromboembolism event (%)	2 (1.5)	0	2 (5.0)	0.09
O blood group (%)	59 (43.7)	42 (44.2)	17 (42.5)	1
<b>Pregnancy characteristics</b>				
<b>Aspirin or heparin use during pregnancy (%)</b>	<b>14 (10.4)</b>	<b>6 (6.3)</b>	<b>8 (20.0)</b>	<b>0.03</b>
Twin pregnancy (%)	5 (3.7)	3 (3.2)	2 (5.0)	0.6
IUGR (%)	58 (43.0)	42 (44.2)	16 (40.0)	0.7
Median gestational age at IUGR diagnosis (WG)	28 (23-33)			
Stillbirth (%)	33 (24.4)	0	33 (82.5)	
<b>Pre-eclampsia (%)</b>	<b>57 (42.2)</b>	<b>47 (49.5)</b>	<b>10 (25.0)</b>	<b>0.01</b>
Severe pre-eclampsia (%)	43 (31.9)	35 (36.8)	8 (20.0)	0.07
HELLP syndrome (%)	22 (16.3)	17 (17.9)	5 (12.5)	0.6
Median gestational age at pre-eclampsia diagnosis (WG)	33 (29-35)			
<b>DIVC (%)</b>	<b>14 (10.9)</b>	<b>2 (2.1)</b>	<b>12 (30.0)</b>	<b>&lt;0.0001</b>
Postpartum hemorrhage (%)	33 (24.4)	19 (20.0)	14 (35.0)	0.08
<b>Gestational diabetes (%)</b>	<b>18 (13.3)</b>	<b>18 (18.9)</b>	<b>0</b>	<b>0.002</b>
Premature rupture of membrane (%)	19 (14.1)	17 (17.9)	2 (5.0)	0.06
Median gestational age at delivery (WG)	34 (29-38)			
<b>Delivery ≤ 34 WG (%)</b>	<b>73 (54.1)</b>	<b>41 (43.2)</b>	<b>32 (80.0)</b>	<b>0.0001</b>
<b>Cesarian section (%)</b>	<b>91 (67.4)</b>	<b>71 (74.7)</b>	<b>20 (50.0)</b>	<b>0.008</b>
Intensive care admission in postpartum (%)	23 (17.0)	13 (13.7)	10 (25.0)	0.1
Median length of stay	3 (1-6)			
Length of stay ≥ 3 days (%)	12 (8.9)	7 (7.4)	5 (12.5)	0.3
Median newborn weight (grams)	1873 (1104-2568)			
<b>Newborn weight &lt; 1000 (grams) (%)</b>	<b>26 (19.3)</b>	<b>8 (8.4)</b>	<b>18 (45.0)</b>	<b>&lt;0.0001</b>
1000 ≤ newborn weight < 1500 (grams) (%)	25 (18.5)	21 (22.1)	4 (10.0)	0.1
1500 ≤ newborn weight < 2000 (grams) (%)	26 (19.3)	20 (21.1)	6 (15.0)	0.5
2000 ≤ newborn weight < 2500 (grams) (%)	25 (18.5)	20 (21.1)	5 (12.5)	0.3
2500 ≤ newborn weight < 3000 (grams) (%)	19 (14.1)	16 (16.8)	3 (7.5)	0.2
Median newborn weight (percentiles)	23 (5-46)			
Newborn weight < 10th percentile (%)	40 (29.6)	25 (26.3)	15 (37.5)	0.2
Neonatal death (%)	7 (6.5)	0	7 (17.5)	
Female newborn (%)	60 (44.4)	43 (45.3)	17 (42.5)	0.9

Continuous variables are expressed as medians, with minimum and maximum values between brackets, and categorical variables are expressed as frequencies (percents). Chi square test or Fisher's exact test were used for categorical variables and Mann and Whitney U test was used for continuous variables. BMI = body mass index; DIVC = disseminated intravascular coagulation; HELLP = Hemolysis, elevated liver enzymes and low platelet; IUGR = intrauterine growth restriction. WG = weeks of gestation.

**Table 2.** Histological characteristics of placental abruption according to fetal outcome

Placental characteristics	All placental abruption n = 135	Placental abruption without stillbirth or neonatal death n = 95	Placental abruption with stillbirth or neonatal death n = 40	p
Median placenta weight (grams)	335 (265-445)			
Median placenta weight (percentiles)	45 (20-65)			
Placenta weight < 10th percentile (%)	40 (29.6)	25 (26.3)	15 (37.5)	0.2
Median feto-placental weight ratio	5.3 (4.4-6.2)			
Abnormal placental set-up (%)	8 (5.9)	4 (4.2)	4 (10.0)	0.2
abnormal umbilical cord (%)	38 (28.1)	26 (27.4)	12 (30.0)	0.8
Retroplacental hemorrhage (%)	104 (77)	70 (73.7)	34 (85.0)	0.2
Chronic features of the retroplacental hemorrhage (%)	79 (58.5)	53 (55.8)	26 (65.0)	0.3
Median percentage of the placenta with indentation	30 (10-50)			
<b>Indentation ≤ 10 % (%)</b>	<b>13 (9.6)</b>	<b>13 (13.7)</b>	<b>0</b>	<b>0.01</b>
<b>Indentation ≥ 30 % (%)</b>	<b>22 (16.3)</b>	<b>5 (5.3)</b>	<b>17 (42.5)</b>	<b>&lt;0.0001</b>
Macroscopic infarcts (%)	72 (53.3)	55 (57.9)	17 (42.5)	0.1
Median number of infarcts	3 (1-5)			
≥ 2 macroscopic infarcts (%)	44 (32.6)	34 (35.8)	10 (25.0)	0.3
Intervillous thrombi (%)	13 (9.6)	7 (7.4)	6 (15.0)	0.2
Subchorial hematoma affecting ≥ 1/3 of the placental surface (%)	3 (2.2)	1 (1.1)	2 (5.0)	0.2
MVM lesions (%)	99 (73.3)	72 (75.8)	27 (67.5)	0.4
Microscopic infarcts (%)	12 (8.9)	6 (6.3)	6 (15.0)	0.2
FVM lesions (%)	19 (14.1)	16 (16.8)	3 (7.5)	0.2
Avascular villi (%)	14 (10.4)	13 (13.7)	1 (2.5)	0.06
Obliterative fetal vasculopathy (%)	5 (3.7)	3 (3.2)	2 (5.0)	0.6
Chorangiosis (%)	32 (23.7)	23 (24.2)	9 (22.5)	1
<b>Excessive fibrin deposition (%)</b>	<b>65 (48.1)</b>	<b>59 (62.1)</b>	<b>6 (15.0)</b>	<b>&lt;0.0001</b>
<b>Any chorioamnionitis (%)</b>	<b>47 (34.8)</b>	<b>39 (41.1)</b>	<b>8 (20.0)</b>	<b>0.03</b>
<b>Any chronic inflammation (%)</b>	<b>34 (25.2)</b>	<b>31 (32.6)</b>	<b>3 (7.5)</b>	<b>0.002</b>
<b>Chronic chorioamnionitis (%)</b>	<b>24 (17.8)</b>	<b>23 (24.2)</b>	<b>1 (2.5)</b>	<b>0.002</b>
Acute chorioamnionitis (%)	25 (18.5)	18 (18.9)	7 (17.5)	1
Chronic villitis/intervillositis (%)	10 (7.4)	9 (9.5)	1 (2.5)	0.3
Chronic deciduitis (%)	5 (3.7)	4 (4.2)	1 (2.5)	1
Funisitis (%)	8 (5.9)	7 (7.4)	1 (2.5)	0.4

Continuous variables are expressed as medians, with minimum and maximum values between brackets, and categorical variables are expressed as frequencies (percents). Chi square test or Fisher's exact test were used for categorical variables and Mann and Whitney U test was used for continuous variables. FVM = fetal vascular malperfusion; MVM = maternal vascular malperfusion.

**Table 3.** Multivariable logistic regression analysis evaluating factors associated with poor fetal outcome among placental abruption.

<b>Pregnancy parameters</b>	<b>Coefficient</b>	<b>Odd Ratio (95% CI)</b>	<b>Z</b>	<b>p-value</b>
Autoimmune disease in mother	1.93	6.93 (0.02-2060.89)	0.66	0.50
<b>Tobacco use during pregnancy</b>	<b>-2.40</b>	<b>0.09 (0.01-1.10)</b>	<b>-1.88</b>	<b>0.06</b>
Aspirin or anticoagulant use during pregnancy	1.30	3.70 (0.11-119.11)	0.73	0.46
HELLP syndrome	-1.22	0.29 (0.01-14.98)	-0.61	0.54
Term at delivery	0.27	1.32 (0.43-4.10)	0.48	0.62
DIVC	1.69	5.44 (0.02-1432.64)	0.59	0.55
<b>Placental macroscopic infarcts</b>	<b>-3.30</b>	<b>0.04 (0.00-0.49)</b>	<b>-2.49</b>	<b>0.01</b>
FVM lesions	0.06	1.07 (0.04-32.53)	0.03	0.96
<b>Placental histological chronic inflammation</b>	<b>-2.66</b>	<b>0.07 (0.01-0.61)</b>	<b>-2.40</b>	<b>0.01</b>

Coefficient column represents the associated coefficient of each variable within the model, Z column stands for the z-value of the parameter (the coefficient divided by its standard error). CI = confidence interval ; DIVC = disseminated intravascular coagulation; FVM = fetal vascular malperfusion; HELLP = Hemolysis, elevated liver enzymes and low platelet.

## **Figures:**

**Figure 1.** Flow chart of the study

**Figure 2.** Image of a placenta microscopic section from a woman with placental abruption showing histological features of chronic chorioamniotitis with macrophages and lymphocytes infiltrate in the chorion (denoted by black arrows). HES stained. (private collection of P. Marcorelles).

**Figure 3.** Images of a chronic retroplacental hemorrhage. **A.** View of the basal plate of the placenta with a voluminous adherent clot. **B.** Transversal section of the placenta: visualization of the indentation of the placenta and of a macroscopic infarct.

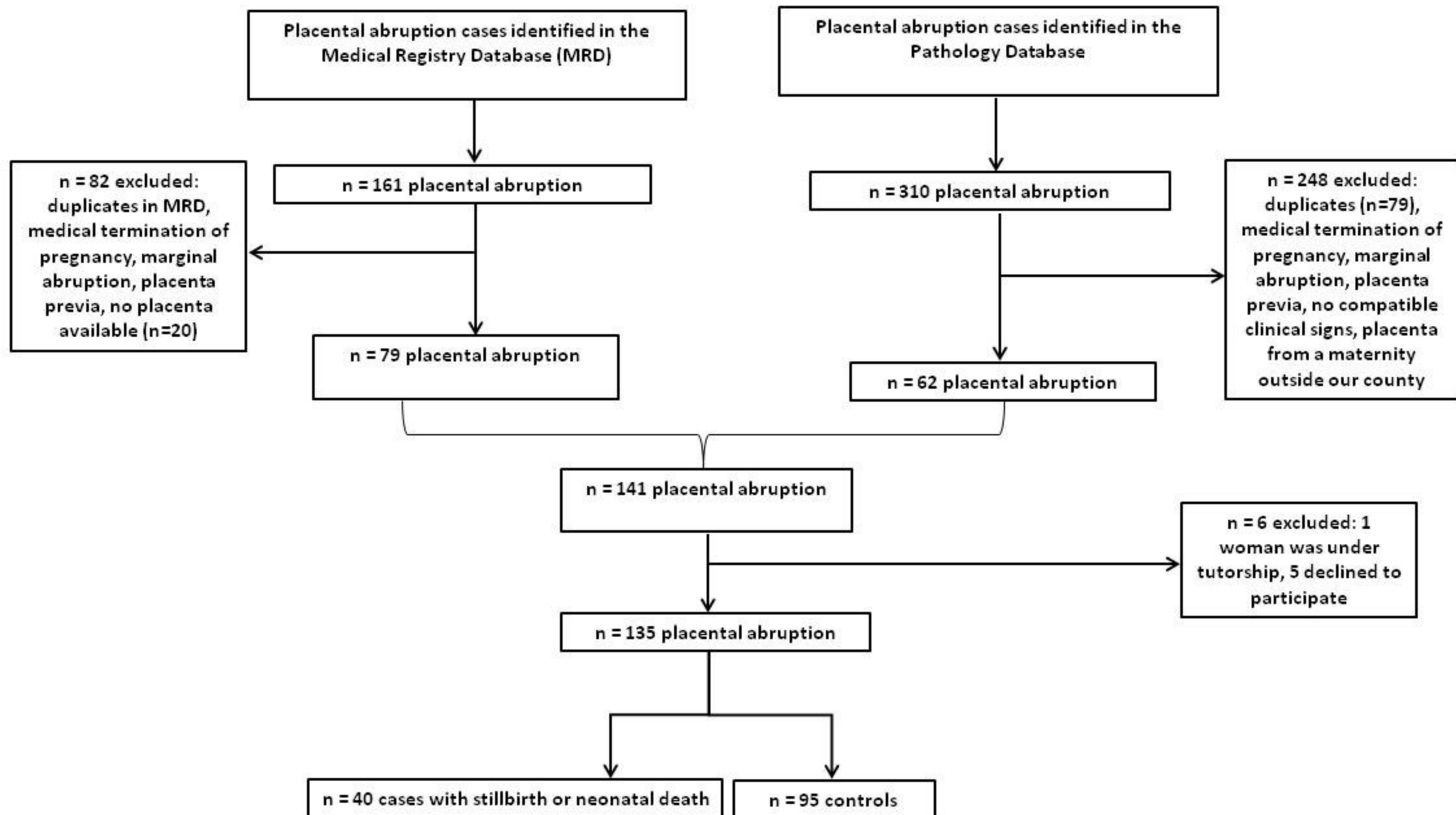
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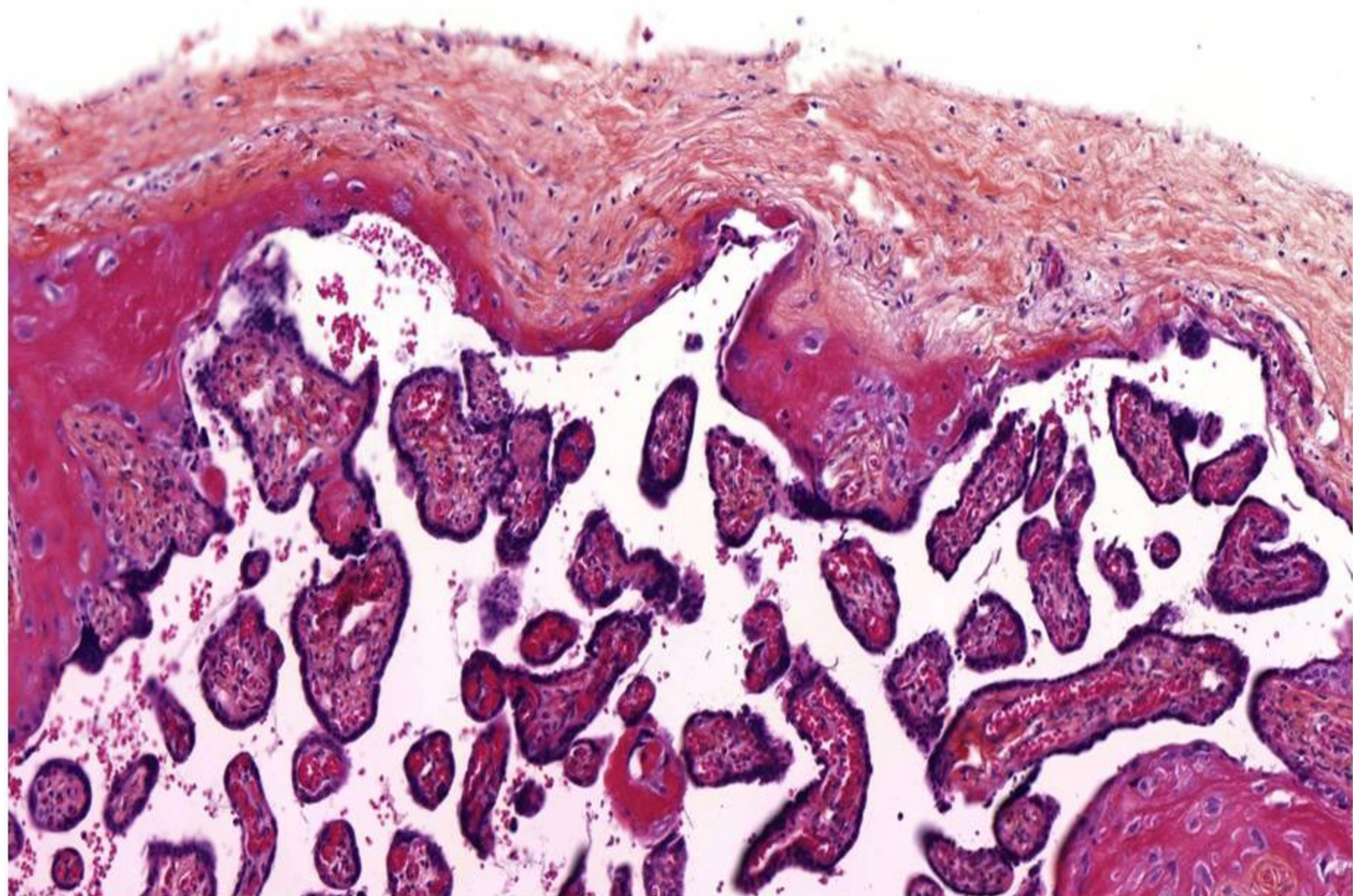
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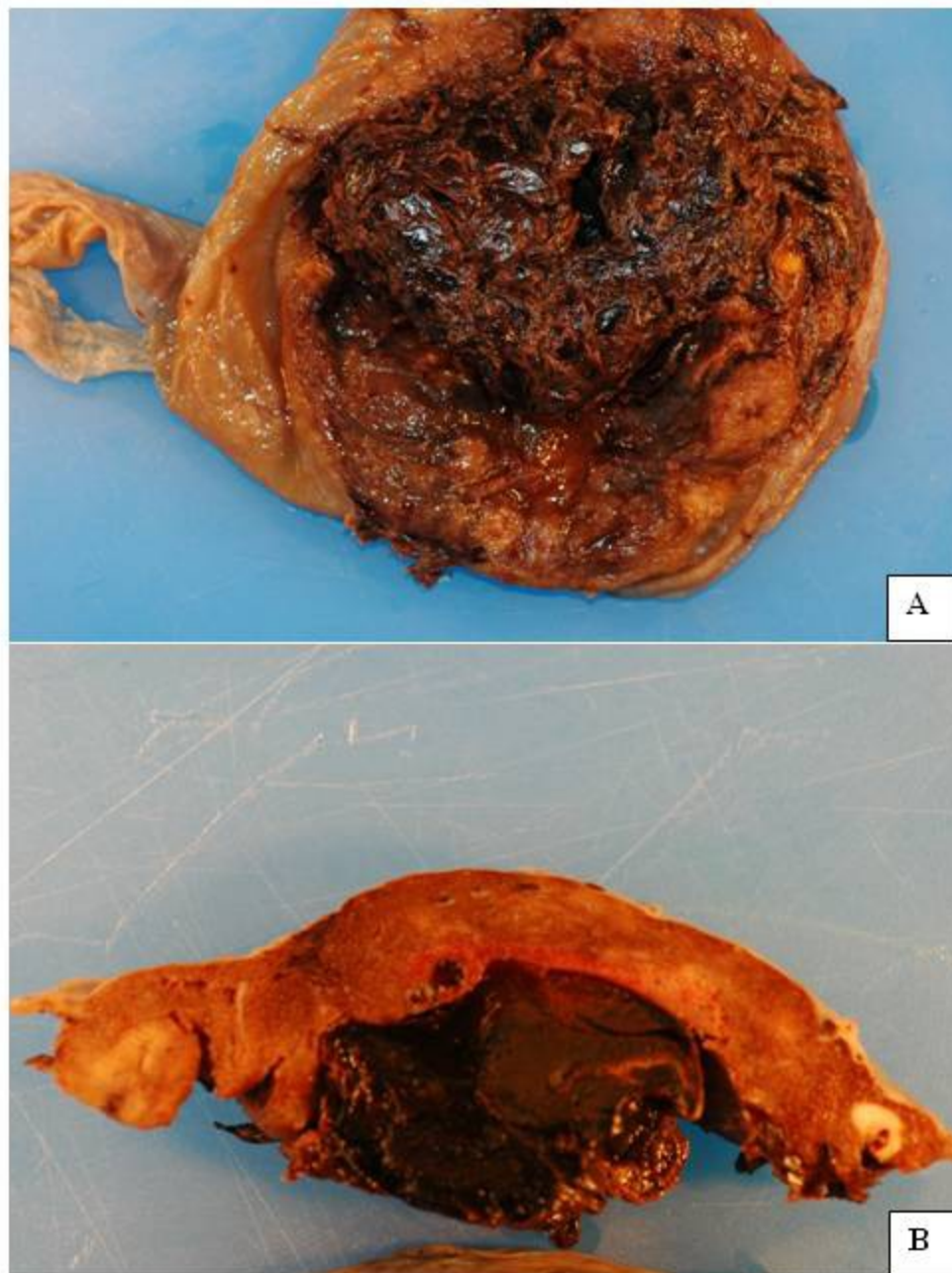
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