ABRUPTIO PLACENTAE IN THE BABOON (*PAPIO* SPP.)

M. Schenone[1], **N. Schlabritz-Loutsevitch**[1,A], **J. Zhang**[2], **J.E. Samson**[1], **G. Mari**[1], **R.J. Ferry Jr**[3,4,5], **G.B. Hubbard**[6], and **E.J. Dick Jr**[7]

[1]Department of Obstetrics and Gynecology, University of Tennessee Health Science Center, Memphis, TN, USA

[2]Department of Pathology, University of Tennessee Health Science Center, Memphis, TN, USA

[3]Division of Pediatric Endocrinology and Metabolism, Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN, USA

[4]Le Bonheur Children's Hospital, Memphis, TN, USA

[5]St. Jude Children's Research Hospital, Memphis, TN, USA

[6]Department of Pathology, University of Texas Health Science Center, San Antonio, TX, USA

[7]Department of Pathology, Texas Biomed Research Institute, San Antonio, TX, USA

Abstract

Introduction—Placental abruption is a serious condition that increases perinatal morbidity and mortality. Clinical prevention and treatment options are limited, especially in human preterm deliveries. Knowledge of the mechanisms that keep the placenta in place during pregnancy is critical for developing strategies for the prevention of abruption. Failure of physiological transformation of spiral arteries has been described as a major contributing factor of the placental abruption development. Baboons (*Papio* spp.) share striking similarities with humans in regard to placental structure, utero-placental blood flow, and fetal development; however, the mode of trophoblast invasion is shallow in baboons. This fact prompted the hypothesis that the incidence of placental abruption will be increased in baboons compared to humans.

Material and methods—Baboon placentas were collected between 2002 and 2008. Two independent veterinary pathologists evaluated the slides. A certified physician pathologist performed additional histology.

Results—Placental abruption was diagnosed in 22 baboons among 2,423 live births during the study period (0.9% prevalence). The most common clinical presentations were fetal demise and vaginal bleeding. The most common pathological findings were intraplacental hemorrhage with or without hematoma formation (86.4%). Other findings consisted of neutrophil infiltration (50%), decidual necrosis (22.7%), decidual vascular congestion and inflammation, villous congestion and retroplacental hemorrhage/hematoma (18.2%). These pathologic findings were the same for term and preterm deliveries.

ACorresponding author: Natalia Schlabritz-Loutsevitch MD, PhD, Assistant Professor, University of Tennessee Health Science Center, Department of Obstetrics and Gynecology, E102 Rout Center for Women and Newborns, 853 Jefferson Avenue, Memphis, TN 38103-2896, Office: (901) 448-4786, Cell: (210) 317-0156, Fax: (901) 448-2626, nschlabr@uthsc.edu.

Conclusion—This is the first systematic study of placental abruption in non-human primates, analyzing a large colony of baboons. Despite differences in trophoblast invasion, the clinical features observed in placental abruption affecting baboons resembled those reported in humans. The cluster of placental pathological findings in baboons also agreed with clinical reports, but the prevalence of these findings differed between baboons and humans. We discuss a mechanism of anti-abruption forces that offset shallow trophoblast invasion observed in baboons.

INTRODUCTION

Placental abruption is defined as the premature separation of a normally implanted placenta (1). In humans, the frequency of this pathology is approximately 0.6%–4% of live, term, singleton, pregnancies (2–5) and is associated with a high maternal and perinatal morbidity and mortality (1,2,4,6). Placental abruption has been extensively studied in humans with several theories proposed to explain its occurrence (7–9). The etiology is still poorly understood (10); consequently, both preventive and treatment measures are limited. The urgent need for identifying such measures is underscored by the fact that placental abruption is a contributing factor in 10% of preterm deliveries (11).

The placental structure and function of Old World non-human primates (NHP) greatly resembles that of humans, including the development of the villous tree, hemochorial placentation, intervillous space (IVS) circulation, and the structure of materno-fetal oxygen barrier (12, 13). Pioneering work by Ramsey et al. detailed hemodynamic parameters for IVS and uterine blood flow in the rhesus monkey (*Macaca mulatta*). These parameters bear striking similarities with humans, despite differences in the depth of trophoblast invasion (14, 15). Excellent reviews regarding differences and similarities in early placentation between human and NHP (*M. mulatta* and *Papio* spp.) describe features like early presence of intravascular trophoblast, superficial implantation and absence of decidual reaction in Old World NHP as compared to humans (12, 16, 17). Data describing premature placental separation in NHP is limited to a few cases of both experimental and spontaneous abruption (18–25). There are no published data available in any NHP regarding the incidence of placental abruption.

Failure of physiological transformation of spiral arteries has been recognized as one of the contributing factors to the pathophysiology of placental abruption in humans (9). Since physiologic trophoblast invasion into the uterine vessels is shallow in baboons (*Papio* spp.) as compared to humans (12), we hypothesized that baboons would have an increased incidence of placental abruption.

The study of spontaneous abruption in NHP may shed some light into the mechanism of such pathology in humans and answer the question: what keeps the placenta in place in the absence of deep trophoblast invasion? In this study we evaluated the prevalence, clinical features, and pathological findings of spontaneous placental abruption in baboons. We further compared our findings with existing human data to discuss potential anti-abruption mechanisms in naturally occurring shallow trophoblast invasion as seen in baboons.

MATERIALS AND METHODS

The baboon colony was maintained by the Texas Biomedical Research Institute at the Southwest National Primate Research Center (SNPRC) in San Antonio, Texas. The SNPRC's Animal Care and Use Committee approved all animal procedures.

Gross evaluation of the placenta and fetus (if available) were performed by pathologists in cases of complicated pregnancies from 2002–2008 as part of the routine pathological

examinations. Placental and fetal weights were recorded and fetal necropsies were performed when possible. Placental abruptions were diagnosed based on clinical and pathological features by a clinical veterinarian and a veterinary pathologist. Maternal age and parity, gestational age and clinical findings at diagnosis were abstracted from the pathology reports and from a computerized animal records database which is part of the Computerized Animal Management Program (CAMP) at the Texas Biomedical Research Institute (San Antonio TX). Placental samples were fixed in formalin and were processed conventionally and 5 μm sections stained with hematoxylin and eosin. Histology was performed by two independent veterinarians and a physician (each certified in pathology by the corresponding North American boards).

Pregnancy was clinically diagnosed using standard criteria previously described for this animal colony. The first day of pregnancy was estimated as the day a female's sexual swelling began to decrease minus two days (26). In cases where the cycle data were not available, pregnancy was dated by ultrasound examination under sedation. In our study, the gestational age at delivery confirmed by fetal biometric information obtained during ultrasound examinations in 6/19 animals (31.6%). Term and preterm pregnancies were categorized as previously described (26). Placental abruption is defined as premature (before birth) separation of the placenta from its normal implantation site (27). Clinical and/or pathological findings consistent with abruptio placentae were used to define these cases in the baboons. In order to facilitate comparison with human data, we excluded 3 cases of clinically and pathologically suspected placental abruption diagnosed before 88 days of gestation. This cutoff best simulates the 20 weeks' gestation cutoff used to diagnose placental abruption in humans. Table 1A lists other fetal and maternal characteristics of analyzed cases. Table 1B describes cases in which abruption was suspected clinically and pathologically, but was excluded due to early gestational age (<88 days' gestation).

Placental efficiency was calculated as the ratio of fetal/placental weights (expressed as $g \bullet g^{-1}$), when these variables were available (28). SPSS was used for statistical analyses. Fisher's exact test was utilized to compare dichotomous variables. A two-sided p-value below 0.05 was considered significant.

RESULTS

Prevalence and risk factors

A total of 2,423 singletons were delivered during the study period with placental abruption diagnosed in 22 baboons (0.9%). The mean gestational age at diagnosis of placental abruption was 143.8 ± 33.6 days. The mean maternal age was 10.3 ± 5.5 years, and the mean number of offspring before the abruption was 3.2 ± 2.5. Most abruptions (16 of 22) were diagnosed during the third trimester of the pregnancy. The mean fetal weight was 728 ± 299.7 grams, and the mean placental weight was 186.1 ± 97.6 grams. In 14 cases in which the fetal gender could be determined, 8 (57.1%) were male fetuses. Clinical presentations in the majority of abruptions (12/22) were intrauterine fetal demise (12 of 22) and/or vaginal bleeding (4 of 22).

Pathological findings

Intraplacental hemorrhage was the most common histopathological finding (86.4%) among abruption cases. Other pathologic findings included: decidual and villous neutrophil infiltration (50%); decidual necrosis (22.7%); as well as decidual vascular congestion and inflammation, villous congestion, and retroplacental hematoma/hemorrhage (each of these affecting 18.2%). Figures 1 and 2 show macroscopic and microscopic pathological findings, respectively, related with these abruptions. One case displayed retroplacental hemorrhage

with hemosiderin-laden macrophages and atherosis of placental bed spiral arteries (Fig. 3). Calculated placental efficiency was 3.9 ± 0.3 g•g^{-1} at term.

Comparison of the prevalence of histopathologic findings between preterm pregnancies and term pregnancies revealed no significant differences between these two groups (Table 2).

DISCUSSION

Prevalence and risk factors in baboon and humans

This is the first large study regarding placental abruption in NHP, considering the limited data available (Table 3). To the best of our knowledge, this is the first comprehensive study, describing spontaneous abruptio placentae in baboons (*Papio* spp.). Stark et al. reported abruptio placentae as a complication of chronic instrumentation in a baboon. Three cases of spontaneous abruption in baboons have been described by Benischke and Miller (19), and the rest of the studies referenced in Table 3 described placental abruption in NHP other than baboons.

Based on the concept of shallow trophoblast invasion in baboon placentation (12, 16, 17), we anticipated an increased occurrence of placental abruption in this NHP. In contrast with our hypothesis, the prevalence of abruption in baboons in this colony was relatively low (0.9%) and comparable to that reported in human pregnancies (1,4,7,8). Various risk factors for placental abruption in humans have been previously described, including prior abruption (the strongest risk factor), acute trauma, smoking, male gender of fetus, preeclampsia, cocaine usage, maternal parity, and snake bites (29). Among these human risk factors, only maternal parity, male gender and acute trauma could be recognized in baboons. One of the limitations of our database relates to the history of placental abruption in the baboon population and documentation of premature rupture of fetal membranes. It is possible that baboons presenting with subtle or chronic clinical signs of abruption might have been misclassified with a different diagnosis, or missed, potentially leading to an underreporting of abruption cases. As in humans, it is possible that some occult abruptions might occur. If external bleeding is not apparent, and animal's (maternal) well-being is not compromised, occult placental abruption may not be diagnosed. In these cases, animals could deliver preterm or at term. The fetal outcome would depend on placental compensatory capacities and the gestational age of the fetus. We are aware that in such cases the placenta abruption would not be noticed and would be recorded as a stillbirth or a normal delivery in the animal database.

Male gender of the offspring has been documented as another risk factor for placental abruption in humans. Similar to these data, in our study, 57% of fetuses delivered after abruptio placentae were males. Placental efficiency in our series was essentially the same to our published control animal data (30), suggesting an acute rather than a chronic event (such as absence of diminished uteroplacental blood flow during pregnancy).

Hypertension (including preeclampsia) and other chronic disorders comprise major risk factors for placental abruption in humans. Preeclampsia and abruption are thought to share pathophysiologic features, such as utero-placental ischemia (10). Data regarding preeclampsia in baboons are controversial. Some authors have reported the presence of experimental preeclampsia in these species (31,32). Others argue that pregnancy-related hypertension does not exist naturally in baboons due to their naturally shallow trophoblast invasion (33). In our colony, blood pressure as well as proteinuria is not continuously controlled; therefore, it was impossible to draw a conclusion in this regard. One baboon, included in this study, developed seizures with a subsequent clinical picture of placental abruption; however, a differential diagnosis of eclampsia was not assessed.

Pathological findings in baboons *vs.* humans

In human pregnancies, two clinical pathways of placental abruption have been proposed: acute (inflammation associated conditions) and chronic (diabetes mellitus, hypertension, smoking, etc.) (29). Pathological findings (such as presence of inflammation, determined by neutrophil infiltration) were noticed with the same frequency in preterm and term deliveries in this study. The differences between human and baboon data could be explained by differences in the incidence of infections between baboons and humans (26). Similar to reports in humans (34), we observed villous congestion with dilation and thrombosis of placental bed blood vessels in the abruption cases studied (Fig. 4).

Although similar pathological features reported in human abruption cases were found in our study, the prevalence between the two species differed. In human abruptions, the most common features seen include retroplacental bleeding (between the placenta and maternal decidua) and poor trophoblast migration with inadequate spiral arteriole remodeling (35, 36, 37). In our baboons, the predominant characteristic was intraplacental hemorrhage (86.4%). Our findings regarding the absence of endovascular trophoblast invasion in the baboon myometrium agrees with the published data (38, 39).

What keeps the placenta in place in the baboon?

Since the depth of trophoblast invasion does not seem to play a critical role in the pathogenesis of placental abruption in baboons, other potential mechanisms must be explored. The increased prevalence of intraplacental hemorrhage in the baboons suggests the possibility that changes in IVS blood flow could contribute to abruption in these species. In a model of artificial placenta, Groeber described IVS blood flow as an essential component of "anti-abruptio forces" (40). IVS blood flow is diminished in human pregnancies complicated by preeclampsia (41) and intrauterine growth restriction (IUGR) (42). Idiopathic IUGR in the baboons has been reported (43). In our study, however 1 out of 10 animals with a recorded birth weight considered had IUGR (446 g at 184 days' gestation) (26). Therefore the likely mechanism in the baboon could be associated with pathology of blood flow redistribution as suggested by Kiss and Tarjan (44). These authors described the subperitoneal plexus as a reservoir for blood shunted from the IVS through the arterio-venous anastomoses during uterine contractions. The increased contractility of the blood vessels or pathologic coagulation impairs this process and results in excessive blood volume within the IVS. This may explain the IVS hemorrhages in the baboon placenta.

Another theory, first suggested by Couvelaire in 1911 (45), links pathology of fetal capillaries to placental abruption, as quoted by Fisher (1964): "*C'est dans le domaine des capillaires que se joue le drame*" (46), or "It's in the domain of the capillaries that the drama is played." Whether these mechanisms are involved in placental abruption in the baboon remains to be elucidated.

In summary, additional research is needed to test the hypothesis that abnormalities in the intervillous space blood flow is an important pathophysiologic factor in placental abruption in baboons and that the regulation of the IVS may be important for pregnancy maintenance in presence of shallow trophoblast invasion.

The main strength of this study is its novelty in the field of the evolutionary pathology of abruption placentae. Baboons comprise an exemplary model for human pregnancy, because of the presence of a discoid hemochorial placenta with an analogous endocrine system. Our subjects were derived from a single baboon colony and all animals corresponded to the genus *Papio* supporting the notion that these pathologic findings correspond to a homogeneous population. Lastly, three certified pathologists analyzed the samples independently thereby decreasing ascertainment bias.

Our study has several limitations inherent to its descriptive design. For example, the study does not include a control population. The pathology of the placentas as well as normal placental development for this baboon colony has been described elsewhere (26, 47). Pathologists were not blinded to the diagnosis of placental abruption. There were no possibilities for continuous blood pressure monitoring or urine analyses in this large baboon colony, which limited our study as well. Data were unavailable regarding history of abruption, a known risk factor for developing placental abruption in humans.

In conclusion, placental abruption in baboons appears to be a relatively rare event (≈1% of spontaneous singleton livebirths at term). Although the prevalence and clinical presentation of placental abruption share common patterns with those observed in human pregnancies, the pathological basis for abruption in baboons may be different. The regulation of the IVS blood flow may be important for pregnancy maintenance in shallow trophoblast invasion.

Acknowledgments

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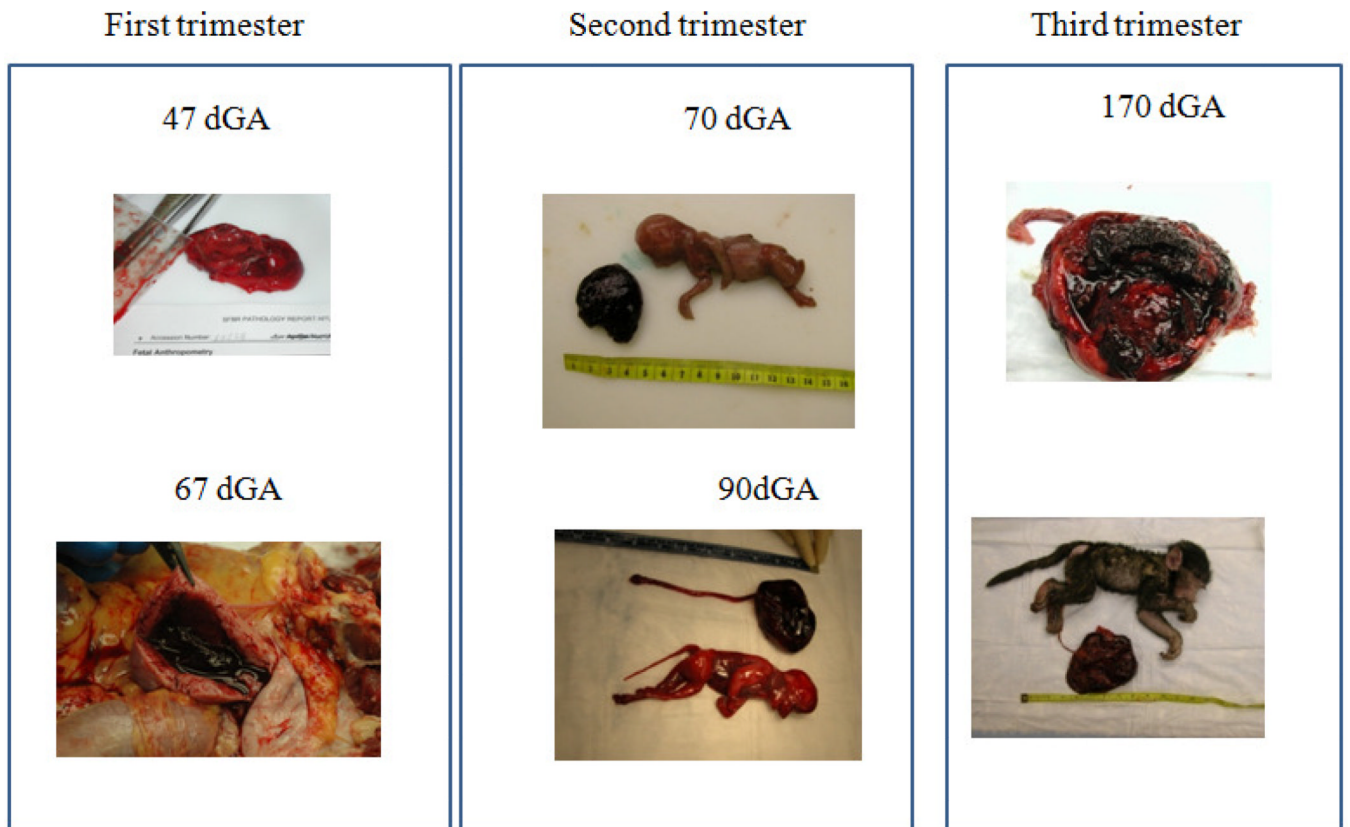
Figure 1.
Macroscopic presentation of placental abruption in baboons (*Papio* spp) at different gestational ages (dGA –Days of Gestation).
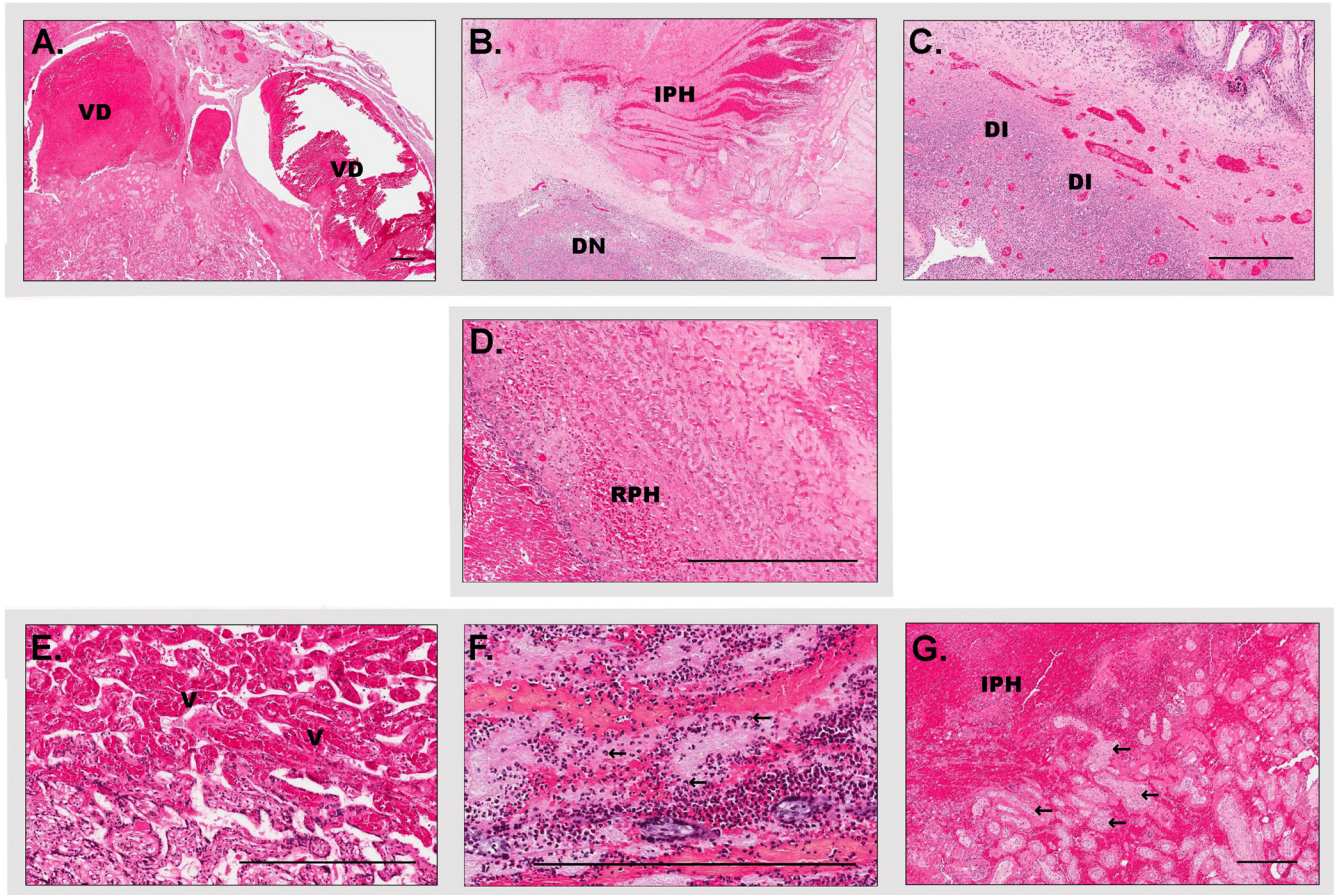
Figure 2.
Microphotographs of the main pathological findings of placental abruption in baboons (*Papio* spp.) A. Decidual vascular dilation (VD). B. Decidual necrosis (DN). C. Decidual inflammation (DI). D. Retroplacental hemorrhage (mild) (RPH). E. Villous congestion (V). F. Villous neutrophils (arrows) G. Intraplacental hemorrhage (IPH) and entrapped villi (arrows), (Scale bar 400 micrometers

Figure 3.
Decidual-myometrial junction in placenta abruption (A) and non-abrupted baboon pregnancies (B). * Decidual artery arterial mural hypertrophy, **- intact decidual artery, arrow – hemosiderin laden macrophages.

Figure 4.
Dilated placental bed vessels in case of placental abruption in a baboon (*Papio* spp.
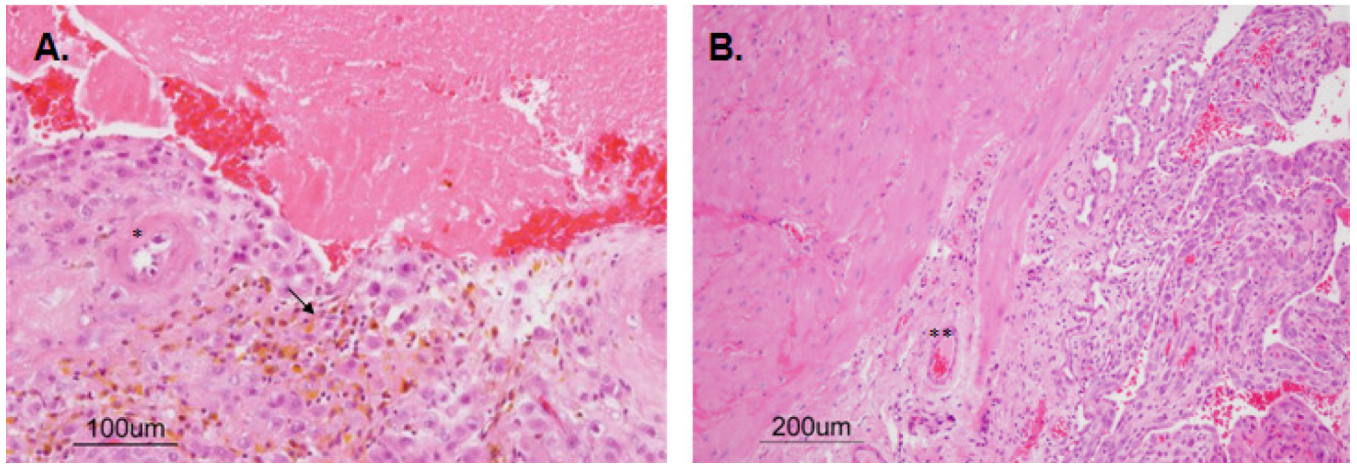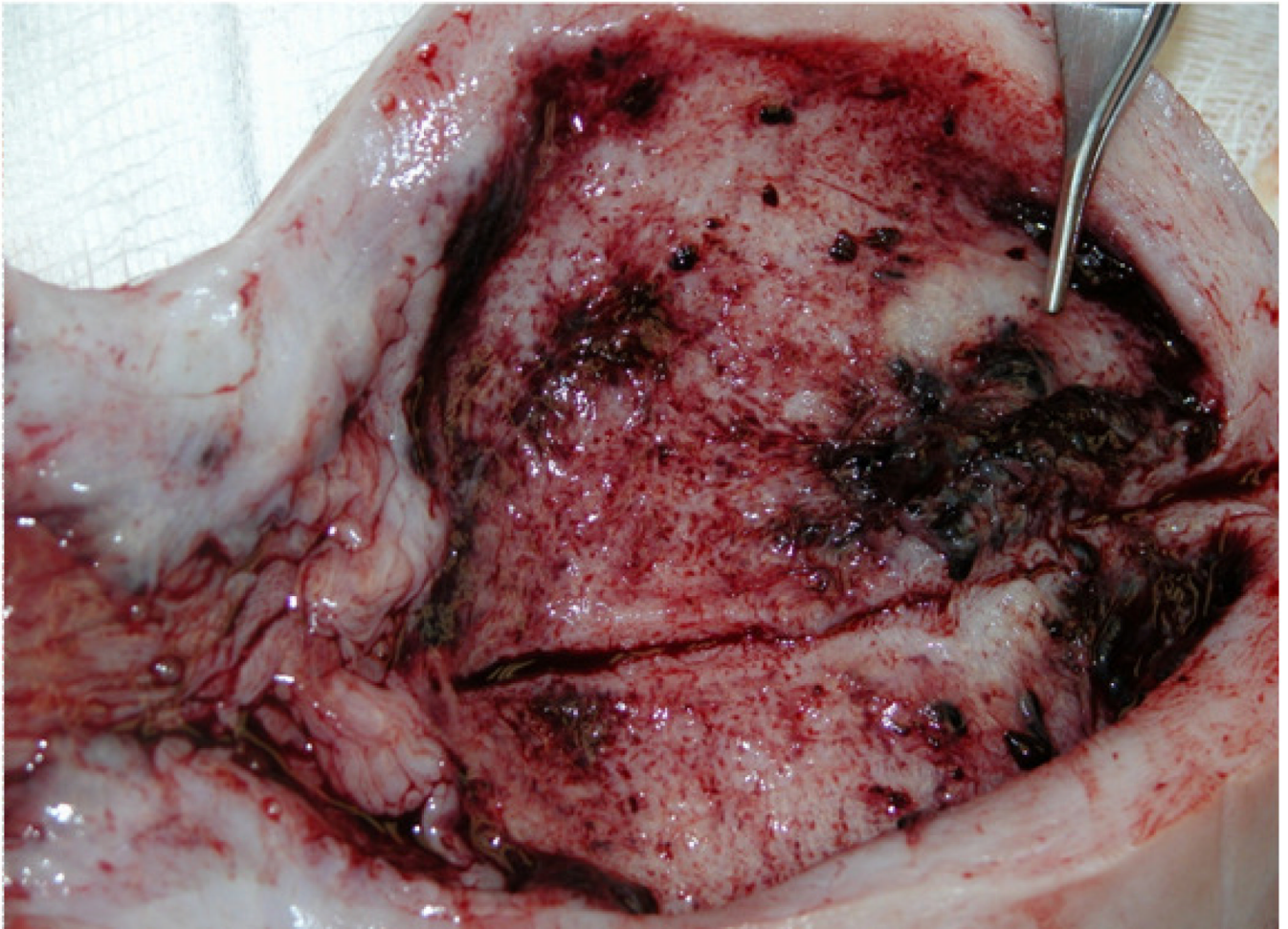
Table 1

A. Fetal and maternal characteristics in cases placental abruption in the baboons (*Papio spp.*) studied

Case	Trimester	Maternal age (y)	Parity 1	Clinical presentation	Gestational age (days)	Fetal gender	Fetal weight (gram)	Placental weight (gram)
1	2	5	0	IUFD	90	U	96	54.4
2	2	9	2	VB	102	U	N/A	82
3	2	16	4	LD and VB	103	U	N/A	N/A
4	2	13	7	VB	110	U	N/A	N/A
5	N/A	8	0	CS	127	U	N/A	N/A
6	3	8	2	CS	128	Male	372	N/A
7	3	10	2	Uterine prolapse	148	Male	704	224
8	3	13	7	IUFD	155	U	N/A	N/A
9	3	12	4	IUFD	156	Female	567	240
10	3	15	5	VB	170	Male	875	317
11	3	12	5	RP	173	Male	1000	277
12	3	13	2	IUFD	178	Male	1018.6	201.10
13	3	14	2	FH	184	Female	446	120.58
14	3	9	4	IUFD	189	Male	982	282
15	3	7	0	IUFD	Term	Female	700	148.35
16	3	17	1	IUFD	Term	U	900	N/A
17	3	7	1	IUFD	Term	U	N/A	N/A
18	3	14	4	LD	Term	U	1248	328
19	N/A	N/A	N/A	IUFD	Term	U	706	N/A
20	N/A	N/A	N/A	IUFD	Term	Female	838	130
21	N/A	N/A	N/A	MC/IUFD	N/A	Female	N/A	N/A
22	N/A	18	8	IUFD/MC	N/A	Female	468	181.5

B. Fetal and maternal characteristics in cases of suspected placental abruption excluded from the statistical analyses

Case	Maternal age (y)	Parity	Clinical presentation	Gestational age (days)	Fetal gender	Fetal weight (gram)	Placental weight (gram)
1	N/A	N/A	Maternal death	47	N/A	N/A	20.4

B. Fetal and maternal characteristics in cases of suspected placental abruption excluded from the statistical analyses

Case	Maternal age (y)	Parity	Clinical presentation	Gestational age (days)	Fetal gender	Fetal weight (gram)	Placental weight (gram)
2	10	4	IUFD	70	Male	32	13.8
3	11	5	Vaginal bleeding	71	N/A	N/A	N/A

[1] Number of offspring before abruption. U : Unknown, IUFD: Intrauterine fetal demise, FH: Fetal hypoxia; VB: Vaginal Bleeding; LD: Labor Dystocia, MC: Poor Maternal Conditions; CS: Finding during cesarean section, RP: retained placenta

IUFD: Intrauterine fetal demise

Table 2

Comparison of pathologic findings between preterm and term diagnosed placental abruption cases

Pathologic Finding	Preterm n (%)	Term n (%)	p-value
Decidual vascular congestion	1(11.1)	2(18.2)	>0.99
Decidual inflammation	2(22.2)	0	0.48
Decidual necrosis	3(33.3)	1(9.1)	0.59
Villous congestion	2(22.2)	1(9.1)	0.93
Intraplacental hemorrhage	9(100)	10(90.9)	>0.99
Neutrophil infiltration	4(44.4)	5(45.5)	>0.99
Retroplacental hemorrhage	3(33.3)	2(18.2)	0.92
Total subjects [*]	9	11	

[*] We were unable to obtain gestational age in 2 of the 22 subjects.

Table 3

Comparison of spontaneously occurring placental abruption previously reported in NHP.

References	Species	n	Risk factors for abruption present	Gestational age (days or trimester)	Clinical features	Pathology	Spontaneous vs. artificially induced abruptio placentae
Present study	*Papio* spp.	22	Trauma, multiparity and humane euthanatia	47–189	Refer to tables 1 and 2	Retro-placental clots	Spontaneous
18	Lion-tailed macaque	1	Multiparity	3rd trimester	Maternal weakness, ataxia, pale mucous membranes, hypothermia and IUFD	10 cm retroplacental blood clot	Spontaneous
19	Mandrill, Gorilla	2	N/A*	Term	Stillbirths	N/A	Spontaneous
20	Gorilla	1	Preeclampsia	Term	Proteinuria documented in the second half of the pregnancy, stillbirth	Small placenta, retroplacental hematomas	Spontaneous
21	*Macaca mulata*	6	N/A	100–120	IUFD of all 6 fetuses	The experimental placental lobe had a dark brown color and showed areas of blood stagnation	Experimental
22, 23	*Macaca mulata*	7	N/A	Near term	2 cases of live births with severe asphyxia and with secondary brain injury 2 cases of incidental finding of placenta abruption on routine CS	IUFD, retroplacental clots and signs of disseminated intravascular coagulation	Spontaneous
24	*Papio* spp.	3	Chronic instrumentation of the fetus	132–142	IUFD , 3 fetuses	N/A	Complication of the experimental procedure
25	*Macaca fascicularis*	2	N/A	> 140	IUFD , 2 fetuses	N/A	Spontaneous

*
Not available, IUFD: Intrauterine fetal demise