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Abruptio placentae in cynomolgus macaques (*Macaca fascicularis*): male bias

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Abstract

Introduction—Abruptio placentae is a serious problem with a high rate of maternal and fetal mortality and documented sexual dimorphism in re-occurrence. *Macaca fascicularis* is a well described reproductive model, however there are no data available regarding sexual dimorphism in abruptio placentae in these species.

Material and Methods—A retrospective study of pathology and medical records in a large colony of *M. fascicularis* was performed. Placental specimens were analyzed.

Results—The incidence of placenta abruptio in the colony was 15.7/1000 births. In the abruptio placentae group, male fetuses had lower placental disk length and increased femur length compared to females fetuses. The fetopacental ratio and fetal weight were lower in the male fetuses in the abruptio group compared to those in the stillbirth group without abruptio placentae.

Conclusion—This is the first documentation of male bias in placental and fetal development in abruptio placentae in non-human primates.

Keywords

placenta; nonhuman primate; pregnancy; complications; sexual dimorphism

INTRODUCTION

Abruptio placentae, occurring in 0.4–1% of human pregnancies, are the part of the great obstetrical syndromes, associated with the pathology of deep placentation in humans (8, 34). The range of perinatal mortality could be as high as 60% (3) and maternal mortality is seven times higher than overall maternal mortality (34, 35). Despite enormous efforts, the etiology of abruptio placentae is still poorly understood. Sexual dimorphism has been described in the incidence of abruptio (36) as well in re-occurrence of this pathology in humans (25).

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The adaptation of the feto-placental unit to adverse maternal conditions differs in male and in female fetuses and this adaptation appears to be species-specific (1). Nonhuman primates (NHP) from the family Cercopithecidae, including baboons (*Papio spp.*) and macaques (*Macaca spp.*) have been extensively used for reproductive studies (17, 20, 23, 27). However, the data describing premature placental separation in NHP is limited to a few cases of both experimental and spontaneous abruptio (6, 20, 23, 30). There are no data available regarding sexual dimorphism in vulnerability of the feto-placental unit in cases of placenta abruption in any NHP. These data are important in understanding the forces that keep the placenta in place during pregnancy and in the development of treatment approaches. The current study focused on clinical and pathological changes in a relatively large cohort of spontaneously occurring abruptio placentae in *M. fascicularis* in comparison to the changes occurring in humans and baboons with emphasis on the effect of fetal gender.

MATERIAL AND METHODS

Animal husbandry

Animals were housed as described previously (31). Briefly, a colony of *M. fascicularis* was maintained by the Southwest National Primate Research Center at the Texas Biomedical Research Institute (SNPRC/TxBiomed) in San Antonio, Texas. Monkeys were housed in metal and concrete indoor/outdoor enclosures. Breeding groups were composed of one breeding male with up to 15 females and their offspring. They were fed commercial monkey chow (Purina Monkey Diet 5LEO, Purina, St. Louis, MO) and given water *ad libitum*. All procedures were done with approval of the SNPRC/TxBiomed Institutional Animal Care and Use Committee.

Record review

Abruptio placentae cases—The clinical and pathological records were analyzed for 2002–2008. Diagnoses of abruptio placentae were based on clinical and pathological findings by clinical veterinarians and veterinary pathologists as described previously (29). Maternal age, parity, gestational age, and clinical findings were extracted from the Computerized Animal Management Program (CAMP) at TxBiomed. Gross and histologic findings were abstracted from the pathology reports and from a computerized pathology database (apath) at TxBiomed; histologic specimens were reviewed as needed. Gestational age was estimated based on the available clinical records, pathology photographs, and femur lengths (33) (Table 1, Fig. 1). Two animals had placental diagnoses consistent with placental abruption; however, these were excluded from the study cohort because of the probability of early gestational age (prior to the equivalent of 20 weeks of gestation in humans).

Stillbirth cases—To compare the placental and fetal morphometry findings in placental abruption cases with the data from the same colony, we also analyzed the stillbirth cases not associated with placental abruption. The detailed maternal characteristics and pathological findings of the animals with stillbirths were previously published (31).

Placental evaluation

Placental samples were fixed in 10% neutral buffered formalin, processed conventionally, sectioned at 5 μ m, and stained with hematoxylin and eosin. Slides were evaluated by two board-certified veterinary pathologists and a medical pathologist.

Statistical methods

The Mann-Whitney exact test was used to compare mean values between genders in the abruptio placentae and stillbirth groups and to compare abruptio placentae vs. stillbirths in the female and male groups. Significance was set at $P < 0.05$.

RESULTS

Maternal characteristics

The incidence of abruptio placentae was 21 cases per 1339 births in the colony of *M. fascicularis*. Average maternal age was 11.5 ± 0.9 years (range 5–18 years), and parity was 4.9 ± 0.6 deliveries (range 1–10) (Table 1). Gestational age, based on femur length could be estimated in 12 animals (11 pregnancies at term: more than 155 days of gestation, and one preterm). Fetal gender distribution was: 47.6% males ($n=10$) and 38.1% females ($n=8$); gender was not available for 14.3% ($n=3$). Maternal clinical and pathological gross diagnoses were unremarkable in most animals (17 of 21), with four pregnancies complicated either by diabetes ($n=1$), dystocia ($n=1$), arm wound ($n=1$), or obesity ($n=1$).

Placental and fetal pathology

Placental and fetal morphometry—Average fetal weight in the second half of gestation was 293.95 ± 19 g (range 150–388 g), and the average placental weight was 83.7 ± 4.2 g (range 44–162 g) with 47.3% of all placentas being bi-discoid. The weight of male and female fetuses at term was similar in the abruption group, and weight of male fetuses was lower compared to the weight of male fetuses in stillbirth group. Placental efficiency (calculated as ratio fetal to placental weight) was lower in the male fetuses of the abruption group compared to the stillbirth group. Fetal femur length was higher and placental disk length was lower in male compared to the female fetuses in abruption group (Table 2).

Pathological findings—The most common placental histological findings overall were necrosis (52.3%), hemorrhage (42.8%), and calcification (23.8%) (Table 3, Fig. 2). We found an increased number of syncytial knots and placental infarction in one animal (Fig. 2A and 2B). In the 11 animals in which gestational age was estimated as more than 155 days of gestation (term), the most common findings were hemorrhage/hematoma (Fig. 2C, 2D, and 2E) and necrosis ($n = 8$ each, 72.7%) followed by villous congestion, neutrophil infiltration, and calcification ($n = 3$ each, 22.7%) (Table 3 and Fig. 2F). The fetal lesions included adrenal necrosis ($n=1$), renal necrosis ($n=1$), pulmonary edema ($n=1$), and brain hemorrhage ($n=1$); no significant lesions were seen in the other seven term fetuses.

DISCUSSION

Incidence, gross anatomy and histology of abruptio placentae

Abruptio placentae is a dramatic obstetrical event described by Couvelaire in 1911 (11) and remains a significant medical issue today (2, 39). The incidence of abruptio placentae in our macaque colony (15.7/1000 deliveries) was higher than that reported in humans (12.1/1000 deliveries) (7) or as estimated in our previous study in baboons (9/1000 deliveries) (29). One possible cause of this discrepancy could be differences in placental blood supply (e.g., absence of anastomoses between uterine arteries in macaques and presence of such anastomoses in baboons) (4, 27). Another possible reason could be the presence of the bi-discoid placentas in macaques compared to single-disk placentas in humans and baboons. A bi-discoid placenta is usually present (80% of pregnancies) in rhesus macaques (23). There appears to be more variation in cynomolgus macaques. The incidence of single-disc

placentas in our study is in agreement with data of Fujiwara *et al.* (16), but higher than 12% published by Ema *et al.* (13) for *M. fascicularis*.

Our pathological findings are similar to those published for baboons (29) and agree with the association between placental calcification, impaired uteroplacental blood flow, and pregnancy complications (including abruptio placentae) reported in humans (10). We previously reported placental calcification in macaques with stillbirths (31). Bunton also found an association of calcification with negative pregnancy outcome in macaques (10). In rhesus monkeys, villous calcification was detected after ligation of interplacental vessels in early gestation (80 days) but not in late gestation (110 days) (28). The presence of necrosis has been published in experimental abruptio in rhesus macaques (24). The increased number of syncytial knots is a novel finding and has not been described in a NHP.

Placental and fetal morphometry: sexual bias

Fall in the placental intravillous space pressure (as seen in abruptio placentae) changes fetal capillary pressure and water content (26), which might cause intrauterine growth restriction. Shimizu (32) found a decrease in biparietal diameter in macaques at least one month prior to pregnancy loss. Consistent with these findings, fetuses in our study had birth weights in the lower range for this population (14). Our findings in macaques differ from baboons, where fetuses born with abruptio placentae weighed within the normal range (29).

The prevalence of male fetuses in abruption cases is consistent with data published on humans and baboons (18, 22). Male gender has been associated with earlier onset of abruption (36) and recurrences of abruption (25) in humans. Such vulnerability of male fetuses is explained by different endocrine responses during pregnancy, genetic determinants (1), and particular HLA class II haplotypes (25). Interestingly, the alleles for HLA class II molecules have different haplotypes in humans and macaques (12) and in the published case report regarding recurrent abruptio placentae in *M. fascicularis* the fetus was a female (30). Thus, it is unlikely, that the HLA-related mechanism would be involved in the sexual bias of abruptio placentae in *M. fascicularis*. Placental efficiency was not affected by stillbirth in humans (38). The decreased placental efficiency in male fetuses in abruption compared to the male fetuses in the stillbirth group might mirror underlying conditions in male offspring in case of placenta abruption (15) and might highlight the structural changes in male placentas, compared to functional changes in the female placentas in the response to the adverse intra-uterine conditions (21). Interestingly, the length of the main placental disc in male fetuses was shorter compared that in female fetuses in abruptio cases. This finding could have a similar mechanism with earlier onset of abruption in human male fetuses (36). It has been suggested, that, in human placentas, the tissues along the length and the breadth of the placenta have different functions (19, 37), where the shorter length of the placental surface was associated with the decreased life span in men (5).

The present study has several strengths such as the analyses of fetal and placental morphometry emphasizing fetal gender, a homogeneous population of *M. fascicularis* living in the same controlled environment, and pathological examination of the placentas by board-certified pathologists. The limitations of the study are the absence of a control population undergoing normal deliveries (explained by placentophagia and necessity of animal sedation to retrieve newborns for morphometry), limited information regarding gestational age at delivery, the retrospective study design, and the probability of missing cases, associated with the limitations of colony management in group housed NHP (29).

CONCLUSION

This is the first report describing the incidence of abruptio placentae and associated placental changes in a large colony of *M. fascicularis*. Despite similarities in placental structure shared by humans, baboons and macaques, the incidence of abruptio placenta in cynomolgus macaques was higher than in humans and baboons. For the first time the male bias in feto-placental development in case of abruption has been documented in non-human primates.

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Figure 1.

A: Second trimester stillborn fetus (F) and placenta (P). B: Third trimester stillborn fetus (F) and placenta (P) with a large retroplacental hematoma (arrow). C: Bi-discoid placenta. D: One-disc placenta. Note areas of hemorrhage (arrow).

Figure 2.

Representative photomicrographs of the placentas from *Macaca fascicularis* diagnosed with placenta abruptio. A: Collapse of the intervillous space (*), villous congestion (arrow) and increased number of syncytial knots (arrowheads). B: Placental infarct (***) with inflammatory cell infiltrates (##) and dystrophic calcification (arrowhead). C and D: Retroplacental hematoma (***) and decidua (D) and inflammatory cell infiltrates (##). E: Intraplacental hematoma (IH) with entrapped villous necrosis (N). F: Extensive dystrophic calcification (arrowheads) and intervillous fibrinoid deposition (pink homogenous material).

Table 1
Characteristics of *M. fascicularis* with the diagnoses of placenta abruptio in the second half of gestation.

	Gender	EGA	Fetal		Placental Weight (g)	Maternal Age (y)	Parity	Maternal Diagnoses	Main Pregnancy-Related Diagnoses		
			Weight (g)						Placental	Maternal	Fetal
1	M	NA	200	50	7	3	Maternal death	Hemorrhage	Dystocia	IUFD	
2	F	NA	360	58	5	1	NR	Necrosis, old abruptio	NA	IUFD	
3	M	Term	288	72	14	9	NR	Abruptio	NA	IUFD, brain hemorrhage	
4	F	Term	372	92	11	7	NR	Abruptio	NA	Neonatal death	
5	M	NA	320	48	NA	1	NR	Abruptio	NA	IUFD	
6	M	Term	118	70	14	7	NR	Old abruptio	NA	IUFD	
7	F	Term	338	70	13	5	NR	Abruptio	NA	IUFD, breech presentation	
8	NA	Term	34 *	44	9	2	NR	Abruptio	NA	IUFD	
9	M	Term	364	70	11	8	NR	Abruptio	NA	IUFD	
10	M	Term	164	106	18	8	NR	Abruptio	NA	IUFD	
11	F	Term	346	162	14	5	NR	Hemorrhage	NA	IUFD	
12	F	Term	321.1	89.1	13	4	NR	Abruptio	Dystocia	IUFD	
13	F	Preterm	288	102	NA	4	NR	Hemorrhage	NA	IUFD, breech presentation	
14	F	Term	382	150	14	7	NR	Hemorrhage	Dystocia	IUFD	
15	F	NA	328	80	NA	4	Diabetes	Abruptio	Shock	IUFD	
16	M	NA	226	60	NA	5	Arm Wound	Abruptio	NA	IUFD	
17	M	NA	388	84	14	8	NR	Hemorrhage	NA	Asphyxia	
18	M	NA	338	78	8	2	NR	Abruptio	NA	IUFD, fetal anoxia	
19	M	Term	294	106	13	10	NR	Abruptio	NA	IUFD, breech presentation	
20	NA	NA	150	NA	NA	NA	NR	Possible Abruptio	NA	IUFD	
21	NA	NA	NA	NA	6	3	Obesity	Abruptio	Dystocia	Live birth	

* Partly cannibalized fetus; NA- information is not available; EGA- Estimated gestational age; Term; more than 155 days of gestation; NR: non-remarkable; IUFD: Intrauterine fetal demise

Placental and fetal morphometry in placenta abruptio group (n=11) and stillbirth group without abruption (n=25) of *M. fascicularis* term pregnancies (more than 155 days of gestation).

Table 2

Fetal parameters	Abruptio placentae group				Stillbirth group			
	Male fetuses		Female fetuses		Male fetuses		Female fetuses	
	n	Mean± SE	n	Mean± SE	n	Mean± SE	n	Mean± SE
Fetal Weight (g)	6	333.61±35.1 ^B	5	266.9±14.6	11	364.59±32.1	14	363.88±63.4
Fetal Length (cm)	6	29.5±0.3	3	27.16±1.1	11	28.86±1.1	14	29.14±2.0
Ponderal Index	6	1.33±0.0	3	1.58±0.2	3	1.53±0.1	8	1.57±0.2
Feto-Placental Ratio	6	4.66±0.6 ^B	5	4.12±0.7	3	6.48±0.9	8	6.29±0.5
BPD (cm)	6	7.01±0.1	3	4.8±2.2	6	5.14±0.2	10	4.98±0.4
Abdominal distance (cm)	6	3.76±0.2	3	3.76±0.4	7	3.73±0.4	11	4.15±0.5
Sternum-to-pubis distance (cm)	6	9.5±0.5	3	10.16±0.7	9	10.72±0.4	14	10.62± 1.1
Femur length (cm)	6	5.12±0.2 ^A	5	4.5±0.2	11	5.01±0.3	15	4.97±0.3
Head Circumference (cm)	4	17.75±0.3	3	16.66±0.3	9	17.28±0.7	11	16.98±0.8
Waist Circumference (cm)	6	10.41±0.5	3	10.83±0.6	9	10.72±0.5	13	11.46±1.2
Hip Circumference (cm)	6	10.33±0.5	3	10.16±0.4	10	11.55± 0.5	14	11.71 ±1.0
Chest Circumference (cm)	6	11.41±0.5	3	12.16±0.7	10	12.50±0.7	14	12.86±1.1
Placental parameters								
Placental weight (g)	5	74.93±5.4	6	67.32±8.1	3	54.46±7.6	8	56.02±8.3
Mean placental disc 1 breadth (cm)	6	6±0	5	8.2±0.9	-	NA	NA	NA
Mean placental disc 1 length (cm)	6	6.5±0.1 ^A	5	9.2±0.9	-	NA	NA	NA
Mean placental disc 2 breadth (cm)	3	6.3±0.7	3	6.5±0.3	-	NA	NA	NA
Mean placental disc 2 length (cm)	3	6.7±0.9	3	7.9±1.3	-	NA	NA	NA
Mean placental disc 1 thickness (cm)	5	1.02±0.2	6	1.22±0.1	2	0.90±0.1	7	0.99±0.1

^A $P<0.05$ compared to the female fetuses in the same group

^B $P<0.05$ compared to the male fetuses in stillbirth group

NA: Information not available; BPD: Biparietal diameter

Table 3Placental pathological findings in placenta abruptio in *M. fascicularis*

Histological Diagnoses	Total Second Half of Gestation (N=21)		Pregnancies at Term (n=11)	
	n	%	n	%
Hemorrhage and thrombosis				
Placental hemorrhage and clot	9	42.8	8	72.7
Placental hemosiderin deposition	1	4.7	0	0
Placental fibrin deposition	1	4.7	0	0
Placental vascular thrombosis	1	4.7	0	0
Fetal membrane hemorrhage	1	4.7	1	9
Infarction and necrosis				
Placental necrosis	11	52.3	8	72.7
Placental infarction	1	4.7	1	9
Placental membrane necrosis	1	4.7	0	0
Inflammatory changes and Infection				
Placental congestion	4	19	3	27.2
Placental neutrophilic infiltration	3	14.2	3	27.2
Placentitis	2	9.5	0	0
Placental fibroblast infiltration	1	4.7	1	9
Placental bacterial colonization	1	4.7	0	0
Placental calcification	5	23.8	3	27.2
No lesion described	4	19	1	9