Acta Scientiarum

http://www.uem.br/acta
ISSN printed: 1679-9291
ISSN on-line: 1807-8648
Doi: 10.4025/actascihealthsci.v39i2.34203

Damage caused by exposure to propofol during gestation of mice

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ABSTRACT. Literature shows that surgical procedure could be necessary at any stage of pregnancy and can cause adverse effects on the mother and fetus. One of the most used anesthetics in surgical centers is propofol however; the safety during pregnancy has not been completely established. The objective of this study was to investigate the possible toxic and teratogenic effects on the intrauterine and post-natal development of mice exposed to the dose of 15 mg kg^{-1} propofol on the caudal vein fifth, tenth and fifteenth day of gestation. A significant reduction in weight gain was observed in female mice who received a 15 mg kg^{-1} dose of propofol on the fifth gestational day. A higher rate of embryonic loss post implantation and resorption was also observed in this group. In regards to physical development, the anesthetic increased significantly the offspring weight gain, the time in which pinna detachment occurred, and the anogenital distance of pups whose females received propofol on the fifteenth day of gestation. Based on these results, we concluded that administration of propofol in the beginning stages of gestation increases the number of abortions and promotes alterations in the physical development of pups whose mothers were anesthetized in the final stages of gestation.

Keywords: propofol, gestation, non-obstetric surgery, embryonic development.

Danos causados pela exposição ao propofol durante a gestação em camundongos

RESUMO. A literatura mostra que o procedimento cirúrgico pode ser necessário em qualquer fase da gravidez podendo causar efeitos adversos sobre a mãe e o feto. Um dos anestésicos mais utilizados nos centros cirúrgicos é o propofol, no entanto, a sua segurança durante a gravidez não foi completamente estabelecida. O objetivo deste estudo foi investigar os possíveis efeitos tóxicos e teratogênicos no desenvolvimento intrauterino e pós-natal de camundongos expostos à dose de 15 mg kg^{-1} de propofol no quinto, décimo **e** décimo quinto dia de gestação. Observou-se uma redução significativa no ganho de peso em camundongos fêmeas que receberam uma dose de 15 mg kg^{-1} de propofol no quinto dia de gestação. Uma taxa maior de perda embrionária pós-implantação e reabsorção também foi observada neste grupo. Em relação ao desenvolvimento físico, o anestésico alterou significativamente o ganho de peso da prole, o tempo em que ocorreu o desprendimento da orelha e a distância anogenital dos filhotes cujas fêmeas receberam propofol no décimo quinto dia de gestação. Com base nesses resultados, concluiu-se que a administração de propofol nos estágios iniciais da gestação aumenta o número de abortos e promove alterações no desenvolvimento físico de filhotes cujas mães foram anestesiadas nos estádios finais da gestação.

Palavras-chave: propofol, gestação, cirurgia não-obstétrica, desenvolvimento embrionário.

Introduction

Approximately 42% non-obstetrical surgeries are performed during the first trimester of pregnancy, 35% in the second and 23% in the third (Reitman & Flood, 2011; Mandim, Ruzi, Bernardes, & Teixeira, 2015). However, the number established for the first quarter may in fact be higher than in reality, since it is possible that early pregnancy may not be confirmed during this period. The incidence and types of surgeries performed in pregnant women was similar to that performed in young women who were not pregnant, and appendectomies were the most common (Van de Velde & De Buck, 2007).

The literature reports that anesthetics affect mitosis, DNA synthesis and induce neuroapoptosis response (Cattano, Young, Straiko, & Olney, 2008). Furthermore, *in utero* exposure to anesthetic of laboratory animals decreased acquiring spatial memory (Palanisamy et al., 2011). These data suggest that fetal brain development can be permanently affected by maternal anesthesia.

Propofol is anesthetic used for induction and maintenance of general anesthesia and sedation for obstetrical and pediatric procedures. Propofol interacts with GABA and glutamate receptors NMDA receptors. (Irifune et al., 2003). It is known

that these receptors were modulated by anesthetics; however, information about the effects of propofol on central neurons is scarce.

In addition, propofol causes the death of brain cells in neonatal experimental animal (Vutskits, Gascon, Tassonyi, & Kiss, 2005; Cattano et al., 2008; Pesić et al., 2009; Bercker et al., 2009; Milanovic et al., 2010) and long-term behavioral deficits in the developing brain (Yu, Jiang, Gao, Liu, & Chen, 2013). Another example of propofol toxicity was verified by Cheng et al., (2010) who found that propofol prevented the proliferation of cardiac fibroblasts, by interfering with the generation of reactive oxygen species.

The safety of the propofol has not been established and the consult literature does not bring anything describing the effects of propofol in embryonic development and postnatal foetus. The objective of the present study was to investigate the toxicity of the drug in the different gestational periods and to evaluate the teratogenic effects on intrauterine and postnatal development of the offspring.

Material and methods

Animals

Swiss female mice (*Mus musculus*), with an approximate weight of 35 g, were maintained in a controlled lighting system (12-hours light / 12 hours dark cycle) at 22 ± 2°C, with water and food freely accessible. The animals were put to mate late in the afternoon in individual cages in a proportion of a female mice to a male mouse. In the following day, with a gap of 12 hours, the vagina of females were examined to verify the occurrence of the "vaginal plug", which would determine the day zero of pregnancy (DG 0). The Ethics Committee on Animal Experiments of the State University of Londrina (Protocol 13035/2008) approved all procedures in this study.

Experimental design

Evaluation of embryo-fetal development

Pregnant females were distributed in three treated groups and three control groups. Each group consisted of 15 animals. The animals of the treated groups received a 15 mg kg^{-1} dose of propofol (PROPOVAN; Cristália, Itapira, Brazil) via the caudal vein on the fifth (group 1), tenth (group 2) and fifteenth day (group 3) of gestation to simulate the use of the anesthetic in a medical intervention during the first, second and third trimester corresponding to the stages of embryo implantation, embryonic period and fetal period respectively. The anesthetic dose used is the one recommended in the literature for mice anesthesia with propofol (Glen, 1980). Mice from the three control groups received a saline solution following the same scheme as the treated groups. Weight gain was monitored and on the eighteenth day, the females were euthanized by cervical dislocation. Procedures of laparotomy and hysterectomy were conducted to analyze embryo-fetal development.

Maternal weight gain (final weight – initial weight), number of resorptions (early and late resorptions were recorded), live and dead fetuses, fetal and placental weight were recorded. The number of implantation sites were determined using Salewski (1964) method. With these data, the rate of resorption (number of resorptions x 100 / number of implantations); rate of post-implantation loss (number of implantation – number of live fetuses x 100 / number of implantations); fetal viability (number of live fetuses x 100 / number of implantations) and the placental index (placental weight / fetal weight) were calculated.

The fetuses were measured by crown-rump length and weighed individually. Half of the fetuses of each litter was fixed in bodian for subsequent visceral analysis (Wilson, 1965). The other half of the litter was fixed in acetone for subsequent skeletal analysis utilizing the alizarin red technique (Staples & Schnell, 1964).

Evaluation of post-natal development

Females mice were distributed in six experimental groups: three treated groups and three control in which each group consisted of 10 animals. In the treated groups, the animals received propofol (15 mg kg^{-1}) through the caudal vein on the fifth, tenth and fifteenth day of gestation. The animals of the control group received a saline solution following the same scheme as the treated groups. The animals gave birth naturally and the litters were reduced to four females and four males to prevent competition of milk.

The day of birth was designed as post-natal day zero (DPN 0). On the first post-natal day (DPN 1), the external morphology of all the offspring was analyzed. The parameters related to physical and reflex development were evaluated according to Alder and Zbinden (1977). The mice were observed daily and weighed on the first, second, seventh, fourteenth and twenty-first post-natal day. The physical and reflex development parameters of 1

male and 1 female randomly selected of each litter was analyzed by the parameters: pinna detachment (starting from DPN 2), appearance of hair (starting from DPN 5), appearance of nipples (starting from DPN 6), upper and lower incisors eruption (starting from DPN 8), opening of the ear canal (starting from DPN 10) opening of the eyes (starting from DPN 12), testicular descent (starting from DPN 16) and opening of vaginal canal (starting from DPN 26). The anogenital distance, the distance from the anus to the base of the genitalia, was determined in pups of both sexes with the help of a caliper on DPN 1 and DPN 21. In addition, the presence of righting reflex posture; negative geotaxis and adult walking reflex were analyzed.

Statistical analysis

In the quantitative analyzes, Student's t-test was used. This test was used to compare the groups corresponding to the same day of treatment between the treated and control groups. The same procedure was appliedin the qualitative data, using Fisher's test. The statistical program used was GraphPad Prism. The level of significance was 5%.The ANOVA test was also used in the quantitative data, comparing the different days of treatment between the groups, verifying if there was divergence between the groups.

Results

Maternal toxicity and intrauterine development

The average weight of the maternal organs of the mice did not present significant alteration in any of the experimental groups (Table 1).

The rate of post-implantational embryonic loss and the rate of embryonic resorption had a statistically significant increase in females in the group anesthetized on the fifth gestational day, DG 5 (Table 2).

With respect to external and visceral morphology, the results showed fetuses with premature opening of the eyes and cleft palate, respectively (Table 3). However, these malformations were rare in occurrence and not considered statistically significant. Skeletal analysis showed lumbar rib and incomplete ossification of the cranial, sternum and supraoccipital bones (Table 3). However, such alterations were considered skeletal variations. The variations are usually reversible changes, characterized by not presenting risks to life and because they involve structural alterations of lesser functional significance. These results are in assent with those obtained by Mazze, Wilson, Rice and Baden (1985) who observed an increase in the frequencies of skeletal variation among the offspring of pregnant mice treated with small doses of the anesthetic isofluorane.

Post-natal development evaluation

The average weight gain per group of the mice whose mothers were exposed to propofol during the prenatal period can be observed (Table 4). The anesthetic significantly increased the weight gain of the pups whose mothers were treated on the fifteenth gestational day.

In relation to the physical and reflex development, the pups whose mothers received propofol on the fifteenth gestational day showed a significant delay in the pinna detachment (Table 5) and an increase in the anogenital distance of the male pups (Table 6).

Table 1. Effects of the treatment with propofol (15 mg Kg^{-1}) on the maternal parameters of mice.

	Control			Propofol		
Number Maternal Mice	15	15	15	15	15	15
Parameters	5th GD	10th GD	15th GD	5th GD	10th GD	15th GD
Total weight gain (g)	21.46 ± 1.81	20.15 ± 0.91	21.71 ± 1.43	20.24 ± 1.56	19.9 ± 1.34	21.48 ± 1.21
Uterus with fetuses (g)	13.24 ± 1.78	13.00 ± 0.79	14.60 ± 1.49	13.90 ± 1.30	13.26 ± 1.44	14.77 ± 1.30
			Organ Weight			
Heart (g)	0.17 ± 0.06	0.16 ± 0.05	0.16 ± 0.06	0.15 ± 0.006	0.15 ± 0.005	0.18 ± 0.06
Lungs (g)	0.21 ± 0.08	0.19 ± 0.06	0.19 ± 0.08	0.18 ± 0.014	0.20 ± 0.006	0.20 ± 0.06
Liver (g)	2.22 ± 0.09	2.11 ± 0.05	2.14 ± 0.08	2.01 ± 0.06	2.00 ± 0.07	2.08 ± 0.07
Kidneys (g)	0.35 ± 0.08	0.32 ± 0.06	0.33 ± 0.01	0.32 ± 0.01	0.34 ± 0.01	0.32 ± 0.01

Data presented as mean values ± SEM. The letters GD mean: gestational day.It was used ANOVA test and t test.

Table 2. Effects of the treatment with propofol (15 mg Kg^{-1}) on the parameters related to intrauterine development of mice offspring.

	Control			Propofol		
Number Maternal Mice	15	15	15	15	15	15
Parameters	5th GD	10th GD	15th GD	5th GD	10th GD	15th GD
Implantations	10 ± 1.11	11.6 ± 0.64	10.06 ± 0.93	9.93 ± 0.72	9.73 ± 0.86	9.26 ± 0.55
Post implantation lost (%)	10.98 ± 6.42	9.68 ± 4.52	9.50 ± 4.56	17.82 ± 5.70*	13.20 ± 6.72	13.31 ± 6.43
Reabsorption (%)	13.80 ± 6.40	13.98 ± 4.13	13.77 ± 4.46	20.12 ± 5.41*	14.81 ± 6.41	14.54 ± 6.22
Placental index	0.07 ± 0.004	0.068 ± 0.01	0.07 ± 0.03	0.07 ± 0.02	0.07 ± 0.003	0.07 ± 0.02
Fetal viability (%)	76.01 ± 6.42	74.31 ± 4.52	72.49 ± 4.56	67.08 ± 5.76	65.78 ± 6.77	62.28 ± 6.51

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	Control			Propofol		
Number Female Fetus	49	45	43	45	40	38
Fetal weight (g)	1.39 ± 0.02	1.48 ± 0.03	1.45 ± 0.02	1.45 ± 0.04	1.41 ± 0,02	1.40 ± 0.03
Fetal length (cm)	2.73 ± 0.03	2.75 ± 0.04	2.76 ± 0.02	2.82 ± 0.03	2.70 ± 0.05	2.67 ± 0.06
Number Male Fetus	49	49	47	44	43	42
Fetal weight (g)	1.42 ± 0.02	1.55 ± 0.05	1.47 ± 0.01	1.44 ± 0.02	1.42 ± 0,02	1.46 ± 0.02
Fetal length (cm)	2.75 ± 0.03	2.77 ± 0.05	2.73 ± 0.03	2.82 ± 0.02	2.70 ± 0.04	2.69 ± 0.04

Data presented as mean values ± SEM. *Statistically significant difference ($p < 0.05$), in both test. It was used ANOVA test and t test. The letters GD mean: gestational day. Ps.: Placental index is the ratio of the weight in grams of the placenta by the weight in grams of the fetus.

Table 3. Visceral, external and skeletal alterations observed in fetuses of female mice treated with proprofol (15 mg Kg^{-1}).

	Control						Propofol					
Fetuses Examined	98		94		90		89		83		80	
	5th GD		10th GD		15th GD		5th GD		10th GD		15th GD	
Anomalies	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
Open Eyes	-	0	1	1.06	-	0	2	2.35	3	3.61	1	1.25
Cleft Palate	1	1.02	-	0	-	0	2	2.35	-	0	-	0
Supermumerary rib	-	0	1	1.06	1	0	1	1.18	2	2.41	2	2.5
IO Sternum	-	0	1	1.06	1	2.22	-	0	-	0	-	0
IO Supraoccipital	-	0	1	2.13	1	2.22	1	1.18	2	2.41	2	2.5

Data present as quantitatively and percentages, on which compared the treatment groups using Fisher test. The letters GD mean gestational day and IO: incomplete ossification.

Table 4. Body weight gain of the mice exposed to propofol (15 mg Kg^{-1}) in the prenatal period.

	Control			Propofol		
Days	5th GD	10th GD	15th GD	5th GD	10th GD	15th GD
1st DPN (g)	1.79 ± 0.07	1.94 ± 0.08	1.81 ± 0.04	1.79 ± 0.04	1.82 ± 0.09	1.97 ± 0.07
2nd DPN (g)	2.20 ± 0.10	2.35 ± 0.11	2.16 ± 0.06	2.12 ± 0.05	2.30 ± 0.10	2.41 ± 0.07^{c,d*}
7th DPN (g)	4.97 ± 0.18	4.74 ± 0.22	5.18 ± 0.31	4.59 ± 0.10	4.84 ± 0.21	5.37 ± 0.18
14th DPN (g)	7.98 ± 0.95	7.69 ± 0.42	8.05 ± 0.25	7.22 ± 0.24	8.15 ± 0.43	9.01 ± 0.34^{a,b,d**,c,e*}
21st DPN (g)	11.90 ± 0.58	12.49 ± 073	12.18 ± 0.50	11.06 ± 0.42	12.17 ± 0.78	14.67 ± 0.68 ^{a,b,c,d,e**}

Data present as mean values ± SEM.The letters GD mean: gestational day, and DPN: post natal day. It was used ANOVA test, followed t test. The statistically significant was indicate by * = $p < 0.05$ and ** = < 0.01. In some results the ANOVA test showed difference between groups, indicated by letters a = 5th GD; b = 10th GD; c = 15th GD and treatment group d = 5th GD; e = 10th GD and f = 15th GD in statistically significant results.

Table 5. Effects of prenatal exposure to propofol (15 mg Kg^{-1}) on the physical and reflexologic development of offspring.

	Control			Propofol		
Fetus Examined	10	10	10	10	10	10
	5th GD	10th GD	15th GD	5th GD	10th GD	15th GD
Phsyical Parameters						
Pinna detachment	3.96 ± 0.14	3.59 ± 0.24	3.96 ± 0.13	4.09 ± 0.21	4.14 ± 0.24	4.42 ± 0.13^{a,b,c*}
Eruption of incisiors	9.78 ± 0.36	9.86 ± 0.26	10.58 ± 0.24	9.72 ± 0.19	10.15 ± 0.12	9.96 ± 0.41
Opening of auditory canal	12.82 ± 0.27	12.25 ± 0.13	12.95 ± 0.19	13.04 ± 0.22	12.63 ± 0.22	12.47 ± 0.24
Opening of eyes	13.83 ± 0.21	13.54 ± 0.14	14.09 ± 0.15	14.31 ± 0.18	13.87 ± 0.22	13.59 ± 0.20
Testicular descent	17.9 ± 0.70	16.7 ± 0.30	17,7 ± 0,33	18,9 ± 0,45	17,3 ± 0,33	17,6 ± 0,40
Opening of vaginal canal	27.2 ± 0.35	27.5 ± 0.40	27.1 ± 034	27 ± 0.14	28.2 ± 0.59	27.5 ± 0.34
Appearance of nipples	9.3 ± 0.26	8.45 ± 0.15	8.3 ± 0.26	9.6 ± 0.42	8.4 ± 0.26	8.7 ± 0.21
	Reflexologic Parameters					
Negative geotaxia	5.45 ± 0.16	5.17 ± 0.22	5.57 ± 0.16	5.57 ± 0.22	5.76 ± 0.23	5.60 ± 0.12
Adult posture	9.25 ± 0.12	9.17 ± 0.06	9.15 ± 0.08	9.43 ± 0.21	9.06 ± 0.04	9.27 ± 0.09

Data present as mean values ± SEM. The letters GD mean: gestational day, and DPN: post natal day. It was used ANOVA test, followed t test. The statistically significant was indicate by * = $p < 0.05$. In some results the ANOVA test showed difference between groups, indicated by letters a = 5th GD; b = 10th GD; c = 15th GD in statistically significant results.

Table 6. Anogenital distance of control and prenatally propofol (15 mg Kg^{-1}) exposed mice.

		Control			Propofol		
		5th GD	10th GD	15th GD	5th GD	10th GD	15th GD
Females	Birth (mm)	1.3 ± 0.09	1.31 ± 0.06	1.12 ± 0.05	1.5 ± 0.16	1.16 ± 0.07	1.18 ± 0.09
	Weaning (mm)	4.2 ± 0.12	4.25 ± 0.33	3.81 ± 0.21	3.79 ± 0.19	4.01 ± 0.21	4.5 ± 0.29
Males	Birth (mm)	2.33 ± 0.10	1.93 ± 0.12	2.15 ± 0.10	2.35 ± 0.19	2.09 ± 0.09	2.1 ± 0.22
	Weaning (mm)	7.92 ± 0.29	7.95 ± 0.46	7.12 ± 0.41	7.28 ± 0.43	7.48 ± 0.36	8.56 ± 0.53^{c,d*}

Data present as mean values ± SEM.The letters GD mean: gestational day, and DPN: post natal day. It was used ANOVA test, followed t test. The statistically significant was indicate by * = $p < 0.05$. In some results the ANOVA test showed difference between groups, indicated by letters control group c = 15th GD and treatment group d = 5th GD in statistically significant results.

Discussion

Maternal exposure to chemical agents during the gestational period can result in changes of the offspring's development. These changes depend on inherent factors in the mother's body, placental function or direct action on the embryo and can cause embryonic and fetal death, malformations, congenital abnormalities and behaviour or physical disability of newborn. The literature related risk of impaired fertility, cleft palate, cardiac abnormalities, miscarriage, premature birth, delayed intrauterine

growth and stillbirths in patients who had been anesthetized in the first month of pregnancy (Reitman & Flood, 2011).

There is an inconsistency in the literature regarding the adverse effects of the anesthetic propofol in relation to obstetric procedures. Although not recommended, propofol is considered safe for pregnant women and is widely used in non-obstetric surgeries and procedures during pregnancy (Ooi & Thomson, 2015). Recent studies in rats have concluded that exposure to propofol during development leads to retardation of physical and neurological reflex, suggesting nervous system injury (Li et al., 2014).

In the present study, it was found that weight gain was significantly reduced when mice were exposed to anesthesia on the fifth day of gestation however; there was no observable symptoms of maternal toxicity. The results suggested that this difference is related to the increase in post-implantation loss rate and the rate of embryonic resorption, which was statistically significant for females, which were exposed to propofol on the fifth day of gestation. The increased resorption rate and post implantation embryonic loss can be consequences of treatment with propofol on the fifth day of gestation, the time the implant is completed (Wang & Day, 2006). Based on this, it can be suggested that the presence of the anesthetic in the maternal circulation of the placenta associated with immaturity caused the occurrence of lethal events for the developing embryo.

Malformations and anomalies observed in fetuses during this research were rare in occurrence and not statistically significant. The fissure palate and open eyes are common malformations in mice and are included in the rate of malformations that are not related to environmental factors and probably have origins in genetic faults and unknown etiology (Niebyl & Simpson, 2008; Gritli-Linde, 2008; Dixon, Marazita, Beaty, & Murray, 2011; Yang et al., 2014).The reduced ossification of cranial bones observed in most experimental animals during the analysis of the skeleton, is considered transient and therefore can not interfere with the development of the offspring.

The manifestation of lumbar ribs is considered spontaneous and not related to treatment. This anomaly is of common occurrence in teratogenic studies of rodents and there is disagreement in the literature as to whether it represents a malformation or not (Damasceno, Volpato, Calderon, Aguilar, & Rudge, 2002). As a teratogenic event is by definition a permanent change (Wichramaratane, 1988), further study would be required to follow the development of additional ribs during adulthood.

The data from the postnatal analysis suggested that exposure to propofol during the prenatal period did not promote change in the weight gain of the offspring belonging to the groups that received anesthesia during the fifth and tenth gestational day. However, pups whose mothers were anesthetized on the fifteenth day of gestational showed significantly higher weight gain and growth in relation to the respective control group. A possible explanation for this finding would be the fact that 15^{th} GD presented the smallest number of pups. Thus, there was a greater supply of nutrients during gestation, favoring the development of the neonate. We did not find in the literature consulted data that relate to the increase of postnatal weight with anesthetics administered during pregnancy.

Besides the weight gain, the other physical parameters that have been altered were the pinna detachment and anogenital distance in male offspring. Gallavan, Holson, Stump, Knapp and Reynolds (1999) has shown the correlation between the anogenital distance and the body weight of the pups, demonstrated in their experiments with rats. The weight of pups, also can be influenced by litter size, maternal toxicity or neonatal toxicity. To minimize this interference, in this experiment, the size of each litter was reduced, for the proposed design (four females and four males).

The alteration of the anogenital distance also can be correlated with hormonal disturbances. As the consume of some substance which can cause endocrine disrupting (Birkett & Lester, 2003; Arnold et al., 2004), or exogenous factors such as the influence of uterine fetus positions during gestation, in which opposite sexes that are neighbours, are influenced by the secretion of different steroids (Richmond & Sachs, 1984). In the consulted literature, there is no report of the relationship of propofol with the endocrine system. Therefore, further studies need to be conducted to evaluate both situations.

Although other studies have reported neurotoxic potential exposure related to Propofol (Yu et al., 2013; Creeley et al., 2013; Yang et al., 2014; Li et al., 2014), according to the results of this study, the anesthetic does not seem to modify the reflection development of the puppies, because there were no differences between the response time for animal control or treated groups.

The main objective of the anesthesiologist is to ensure a safe anesthesia for pregnant women and simultaneously minimize the risk of premature birth or miscarriage (Mhuireachtaigh & O'Gorman, 2006). According to Reitman and Flood (2011), in cases of pregnancy, the anesthesiologist should avoid

fetal exposure to unnecessary medication and regional anesthesia is usually preferred when it is practical for medical and surgical conditions.

Actually, the Guideline published by the UK National Collaborating Centre for Acute Care recommended pregnancy test for women in reproductive age.

It is difficult to measure whether the change observed in the newborn comes from the exposure to anesthesia or surgical procedure. In this present study, pregnant females received anesthesia and did not undergo any surgical procedure; therefore, all changes observed here are due to exposure to anesthetic.

Conclusion

The results of this study show that propofol administration causes an increase in resorption and post-implantation loss in anesthetized female in early pregnancy and promotes an increase in the anogenital distance of male offspring, delays pinna detachment and weight gain of pups whose mothers were anesthetized in late pregnancy. Results obtained in this study and in the literature on events observed in fetuses after maternal exposure to anesthetics, suggest that pregnancy test should be strongly recommended to women who are of childbearing age who would undergo a surgical procedure making use of anesthetics.

Acknowledgements

The Araucária Foundation supported this work.

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Received on November 11, 2016.
Accepted on March 3 2017.