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FEED RESTRICTION DURING PREGNANCY: EFFECTS ON BODY CONDITION AND PRODUCTIVE PERFORMANCE OF PRIMIPAROUS RABBIT DOES

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Abstract: This study examined the effects of feed restriction at different stages of rabbit pregnancy on body condition and productive performance. Just after insemination, pregnant primiparous New Zealand White does were assigned to 4 groups (10/group): the control group (C) was fed with 130 g/d of commercial feed while the others received 90 g/d from day 0 to 9 (R1), from day 9 to 18 (R2) or from day 19 to 28 (R3) of pregnancy and 130 g/d the remaining periods. A 3-point scale for loin and rump was used to calculate the aggregate body condition score (BCS), while perirenal fat weight (PFW) was estimated by ultrasound measurement of its thickness. The C does showed a positive balance of the pregnancy (0-26 d) for both body weight ($P<0.001$) and PFW ($P<0.01$). In particular, these increases occurred in the first 18 d of pregnancy (BW: $P<0.001$; PFW: $P<0.05$). The R1 does showed compensatory body growth after feed restriction (10-18 d: $P<0.01$), but lower BCS ($P<0.05$) at 26 d compared to control group. Feed restriction in mid and late pregnancy determined negative PFW balance (0-26 d: $P<0.05$), lower BCS at 26 d (R2: $P<0.05$) or lower BW gain compared to control (R3: $P<0.05$). The effects of feed restriction on productive performance depended on the restriction period: while R1 does did not show any differences compared to C, restriction during the last third of pregnancy increased perinatal (9.9 *vs.* 16.1%; $P<0.05$) and pre-weaning mortality (10.6 *vs.* 36.7%; $P<0.01$). However, milk production was lower in all restricted groups (C: 156, R1: 132, R2: 133; R3: 124 g/d; $P<0.001$, respectively). Thus, the energy deficit due to concurrent undernutrition and metabolic demands during pregnancy has short- and long-term consequences on both mother and offspring.

Key Words: pregnancy, feed restriction, reproductive performance, body condition, rabbit.

INTRODUCTION

Nutrition during pregnancy influences not only foetal growth but also postnatal development of kits. Undernutrition is caused by imbalance between dietary intake and nutrient requirements. In women, it can be due to severe dieting or eating disorders, such as anorexia, while in animals it is due to inadequate dietary levels, as in intensive farming systems, or lack of food availability, as in wildlife (Kauffman *et al.*, 2010). Low energy supply can affect several aspects of pregnancy and lactation, resulting in delayed implantation, reduced foetal growth, abortion or pre-term birth, malformation, low birth weight of offspring and diminished milk supply (Cappon *et al.*, 2005; Maertens *et al.*, 2006; Matsuoka *et al.*, 2012; García-García, 2011). In addition, maternal undernutrition may also reduce foetal adiposity, which is a critical aspect in determining heat production at birth and thus perinatal mortality. All these consequences strongly depend on the stage of pregnancy at which the undernutrition occurs (Matsuoka *et al.*, 2006; Kauffman *et al.*, 2010). Furthermore, energy deficit during pregnancy can increase the risk for a variety of adult-onset diseases, such type 2 diabetes and obesity (Brecchia *et al.*, 2009; Fischer *et al.*, 2012).

The rabbit is an attractive experimental model to study the effects of undernutrition during pregnancy (Fischer *et al.*, 2012). Some authors have evaluated the effects of feed restriction or undernutrition during rabbit pregnancy on feed

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intake, productive performance (Rommers *et al.*, 2004b; Manal *et al.*, 2010; Nafeaa *et al.*, 2011), organogenesis (Cappon *et al.*, 2005), placental development (Matsuoka *et al.*, 2012) and some blood parameters (Matsuoka *et al.*, 2009). However, evaluation of body condition is needful not only because it is correlated to short- and long-term reproductive efficiency, but also to animal health and welfare (Castellini *et al.*, 2010; Sánchez *et al.*, 2012; Pascual *et al.*, 2013). Thus, an accurate assessment of body condition and nutritional status of rabbit does ensures (i) the identification of stress-related situations perturbing physiological homeostasis; (ii) high-welfare farm management; and (iii) the prevention of unsuccessful insemination (Cardinali *et al.*, 2008; de la Fuente and Rosell, 2012; Pascual *et al.*, 2013). Several non invasive methods to evaluate the body condition and energy balance of female rabbits have been validated. Among these, the most utilised techniques are the body condition score (BCS), a subjective method widely used for livestock such as ewes, cows and sows, and ultrasound measurements of the perirenal fat thickness, which is the main tissue reserve of rabbits (Pascual *et al.*, 2002a; Dal Bosco *et al.*, 2003; Cardinali *et al.*, 2008; Sánchez *et al.*, 2012).

This study assesses body condition during pregnancy with non invasive techniques and assumes that moderate feed restriction during different periods of gestation alters body conditions and productive performance of rabbits.

MATERIALS AND METHODS

Experimental design

Sixty-four pregnant primiparous, non-lactating does (New Zealand White selected by ANCI-National Association of Italian Rabbit Farmers) of 22-26 wk of age, weighing 4.06±0.05 kg, with a perirenal fat weight of 11.2±1.5 g and a BCS of 1.9±0.2 were used. The animals were housed individually in flat deck cages. The temperature ranged from +15 to +28°C, and the light schedule was 16 L:8 D. Ovulation was induced by injection of 10 µg of synthetic gonadotropin-releasing hormone (GnRH; Receptal, Hoechst-Roussel Vet, Milan, Italy) just before artificial insemination (AI) (Brecchia *et al.*, 2006). The day of AI was designated as day 0. After AI, does were randomly assigned to 4 groups (16 does/group) according to the feed restriction treatment. Pregnancy was diagnosed by manual palpation 10 d after AI. Non-pregnant and supernumerary pregnant does were excluded from the experiment in order to obtain a balanced design (10 pregnant does/group). The control group rabbits (C) were fed a standard ration (130 g/d) of commercial food containing 10.9 MJ digestible energy (DE)/kg, estimated according to Maertens *et al.* (1988), and 18.7% crude protein throughout the gestation period. The control diet was formulated to supply approximately 1.2 times the DE requirement for pregnant does according to Xiccato and Trocino (2010) (430 kJ DE/kg body weight $[BW]^{0.75}$). Rabbits in the other 3 groups were fed a lower amount than the energy requirements (90 g/d, i.e. approximately 0.8 times the maintenance requirements) of the same feed, from day 0 to 9 (R1), from day 9 to 18 (R2), or from day 19 to 28 (R3) of pregnancy. Before and after these restriction periods, the pregnant does were fed the standard daily control group ration. Following parturition, lactating does were fed *ad libitum*. Feed intake was recorded daily until the end of pregnancy.

The experimental procedures were carried out according to IRRG recommendations (2005) at the experimental rabbit farm of the Department of Agricultural and Environmental Sciences of the University of Perugia.

Body condition evaluation

In the last 3-4 d of pregnancy, no manipulation was carried out on does so as not to interfere with their welfare during nest preparation. Thus, the BW of each doe was measured on days 0, 4, 10, 14, 18, 22, and 26 of pregnancy using an electronic scale (model Isolad - Vignoli - Forli, Italy). The fat thickness of the perirenal regions (3 cm ahead of the 2^{nd}-3^{rd} lumbar vertebrae) was determined on the same days by ultrasound scanning (ALOKA model SSD-500) after careful shaving of the area. The perirenal fat weight (PFW) was estimated as described by Dal Bosco *et al.* (2003). On the same days, the BCS (0-2 score) of loin (vertical bone protrusions - spinous process - and muscle fullness over and around the vertebrae) and rump (bone protrusions and muscle fullness) was evaluated and summed to obtain an aggregate value (from 0 to 4) (Cardinali *et al.*, 2008). The BCS of each doe was evaluated by 2 experienced technicians and the mean scores were recorded.

Productive performance

Within 24 h after birth, the number of suckling kits was adjusted to 7-10 per litter within each group; the young rabbits were weaned at 28 d. The following productivity indexes were calculated: prolificacy, number born alive, litter weight at kindling, perinatal and pre-weaning mortality, litter size and weight at weaning. Daily milk production was measured from parturition until day 18 of lactation, by weighing the doe immediately before and after suckling. The daily nursing time was 5-10 min.

Statistical analysis

BW, PFW and BCS were analysed using Mixed Analysis of variance (ANOVA) by General Linear Model procedure. The model included the group as between-subject factor (4 levels: C, R1, R2, R3), time as within-subject factor (6 levels: 4, 10, 14, 18, 22, 26 d) and BW, PFW or BCS at the day of IA (0 d) as covariate. These models evaluated the main effects of group and time and the interaction between group and time. Assumption of independence of covariate and group effect was tested by running ANOVAs (Field, 2009). The initial BW, BCS and PFW were not affected by group. These results mean that it is appropriate to use them as covariates. When a significant time by group interaction was found, simple effect analysis with Bonferroni adjustment was conducted to describe the changing group effects across time (Field, 2009). Tests for linear (straight-line relationship) and quadratic (U-shaped relationship) trends of means over time were performed using the orthogonal polynomial comparisons method (Field, 2009). Milk production data were analysed by linear mixed model procedure. In this model, animals were treated as random effects while group, day, and interaction represented fixed effects. Number of kits was not treated as a covariate because ANOVA demonstrated the violation of the assumption of its independence from group effect. Intercept for fixed effects was included in the model. The chi-square procedure was used to analyse mortality rates and one-way ANOVA for the other productive parameters (duration of gestation, litter size, doe and litter weight). Pearson test (r) was used for correlation analyses. Statistical analyses were performed with SPSS Statistics version 20 (IBM, SPSS Inc., Chicago, IL, USA). Statistical significance was set at $P<0.05$.

RESULTS

Until day 28 of pregnancy, all does consumed their rations completely. Furthermore, the reduction of feed intake that occurred in the last 3 d of pregnancy was not significant and there were no differences between the groups.

Body condition

The effect of time on BW and PFW differed among groups, as suggested by the interaction observed between group and day of pregnancy (BW: $P=0.001$, data not shown; PFW: $P<0.05$, Figure 1). Body weight increased progressively during pregnancy in the C, R1, and R2 groups ($P<0.001$; P for linear trend<0.01); in R2 group there was also a significant quadratic pattern in BW across pregnancy ($P<0.05$). The day of gestation influenced also the PFW of C, R2, and R3 groups ($P<0.05$. Figure 1), but in a more complex way because a linear trend was found only in C group (P for linear trend<0.05). A clear effect of group was observed at day 10 of pregnancy for BW ($P<0.05$; data not shown) and at days 22 ($P<0.05$) and 26 ($P<0.01$; Figure 1) for PFW. During pregnancy (from day 0 to 26), body

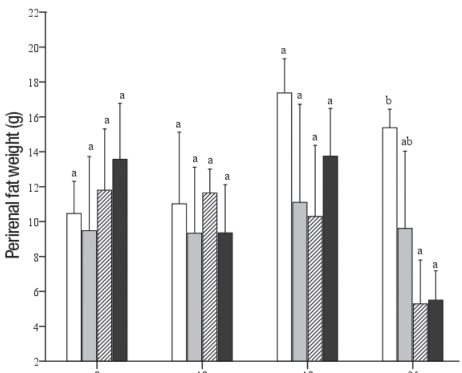

Figure 1: Perirenal fat weight at different gestational days in does receiving control diet (C; n=10) and does subjected to restriction in early (R1; n=10), mid (R2; n=10), and late pregnancy (R3; n=10). Values are means+standard error of the means. Bars not sharing any superscript within each time are significantly different at $P<0.05$.

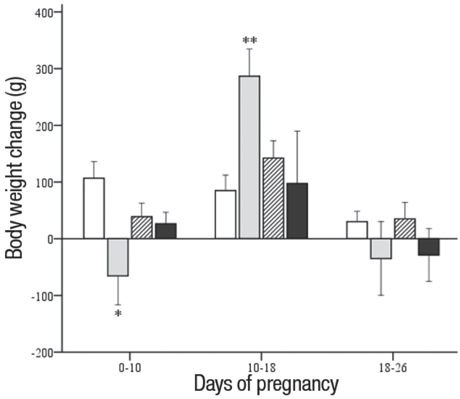

Figure 2: Doe body weight changes during different gestational periods (0-10, 10-18, and 18-26 d of gestation) in does receiving control diet (C; n=10) and does subjected to restriction in early (R1; n=10), mid (R2; n=10), and late pregnancy (R3; n=10). Values are means+standard error of the means. Asterisks indicate significant (* $P<0.05$; ** $P<0.01$) difference compared to control group by Bonferroni's test.

and perirenal fat weight of the control does increased 222 g ($P<0.01$; Figure 2) and 4.91 g ($P<0.01$; Figure 1), respectively. These increases occurred in the first 18 d of pregnancy for both BW (+190 g, $P<0.01$; Figure 2) and PFW (+6.91 g, $P<0.05$; Figure 1). In the last days of pregnancy (days 18-26), changes were not significant.

The R1 rabbits lost body weight (–66 g, $P<0.05$) during the restriction period (0-10 d) followed by a rapid increase after re-feeding with the standard ration (10-18 d: +287 g; $P<0.01$; Figure 2). As mentioned above regarding PFW, time was not significant within the R1 group (Figure 1). In contrast to the C group, BW (mean difference=187 g; $P=0.30$) and PFW (mean difference=0.13 g; $P=1.00$) at day 26 did not differ significantly compared to day 0.

There was no compensatory growth in R2 (18-26 d; Figure 2), while it was not evaluated in R3 because the re-feeding occurred mainly in the *post-partum* period. In the R2 group, after 26 d of pregnancy, BW increased compared to day 0 (+216 g, $P<0.05$); in R3 does, at the same time point, the BW increase was not significant (+95 g, $P=0.29$) and also lower compared to control rabbits (222 *vs.* 95 g, $P<0.05$). In late pregnancy, from 18 to 26 d of gestation, PFW decreased in both R2 and

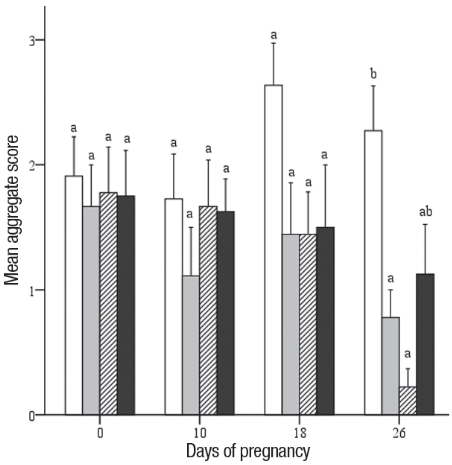

Figure 3: Aggregated body condition score at different gestational days of control group (C; n=10) and of does subjected to restriction in early (R1; n=10), mid (R2; n=10), and late pregnancy (R3; n=10). Values are means+standard error of the means. Bars not sharing any superscript within each time are significantly different at $P<0.05$.

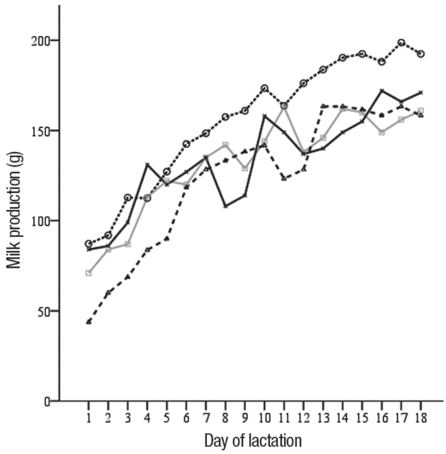

Figure 4: Milk production from d 1 to 18 *post-partum* of control group (C; n=10) and of does subjected to restriction in early (R1; n=10), mid (R2; n=10) and late pregnancy (R3; n=10). Values are means. Milk production was influenced by time ($P<0.001$) and group ($P<0.001$) while interaction was not significant ($P=0.99$).

Table 1: Performance of control group (C; n=10) and of does subjected to restriction in early (R1; n=10), mid (R2; n=10), and late pregnancy (R3; n=10). The results concern the gestation period (duration), kindling (size and weight litter, mortality), lactation period (milk production) and weaning (size and weight litter, mortality). After birth, the number of suckling kits was adjusted, so the values at weaning were calculated starting from adjusted litter size. Values are means and percentage for mortality.

	Experimental treatments					
	C	R1	R2	R3	SEM[1]	*P*-value
Duration of gestation (d)	31.6	31.3	30.8	30.6	0.9	0.31
Litter size at kindling[2] (n)	7.9	9.0	9.3	6.2	2.4	0.15
Kits born alive per litter (n)	7.1[ab]	8.3[ab]	9.1[b]	5.0[a]	2.5	0.050
Litter weight at kindling (g)	402	472	426	348	120	0.20
Weight of individual kit (g)	55	58	51	62	12	0.55
Perinatal mortality[3] (%)	9.9[b]	7.9[b]	1.5[a]	16.1[c]		0.044
Weight of doe after kindling (g)	4277	3871	4016	4029	295	0.096
Litter size at weaning[4] (n)	6.6	6.7	6.6	6.3	2.2	0.20
Litter weight at weaning[4] (g)	2507	2272	2096	2333	394	0.24
Pre-weaning mortality[3,4] (%)	10.6[a]	9.6[a]	27.0[b]	36.7[b]		0.002
Weight of doe at weaning (g)	4402	4031	4133	4427	299	0.13
Milk production[5] (g/d)	156[b]	132[a]	133[a]	124[a]	11	<0.001

Values followed by the same letter in each row do not differ significantly ($P<0.05$; Bonferroni's multiple comparison test).
[1] Standard error of the mean, n=10.
[2] Kits born dead included
[3] Significance from chi-square test
[4] Calculating starting from the adjusted litter size
[5] Measured from parturition until day 18 of lactation.

R3 groups by –5.9 and –8.3 g, respectively ($P<0.05$; Figure 1). In addition, their PFW balance (0-26 d) was negative (R2: –6.5 g; R3: –8.1 g; $P<0.05$).

BCS was affected by group ($P<0.05$), time ($P<0.001$), and time×group interaction ($P<0.01$). In particular, in late gestation, R1 and R2 groups showed lower values compared to control (Figure 3). There was no correlation between body weight and BCS in any group (data not shown).

Productive performance

The average fertility was 65.2% and there were no differences between groups. Undernutrition, particularly in mid and late pregnancy, affected live born (P=0.05), perinatal ($P<0.05$) and pre-weaning mortality ($P<0.01$) (Table 1). Two does from R3 and one from C group aborted. There were no differences in the duration of pregnancy or in the presence of malformations in born rabbits. Milk production was greatly influenced by day of lactation ($P<0.001$) and by treatment ($P<0.001$). Milk production was lower ($P<0.001$) in all restricted groups compared to the control (Table 1), but the lactation curves were similar in all groups (Figure 4) with no interaction (P=0.99).

DISCUSSION

Body condition

Our study overlapped 2 conditions that can alter the internal milieu, pregnancy and feed intake restriction. A complex regulation of energy homeostasis occurs during pregnancy, when adaptive metabolic processes intervene to enhance available energy for foetal growth and accumulate fat storage to support future lactation. Maternal diet can alter this delicate balance and moderate feed restriction may not ensure adequate nutrition for foetuses and/or not provide the necessary reserves to face subsequent lactation. In our study, the overall balance of body and perirenal fat weight of control does was still positive. In fact, as also reported for others mammals (Augustine *et al.*, 2008), during pregnancy the female rabbit accumulates fat reserves for the final foetal growth and subsequent lactation (Pascual *et al.*, 2013). Interestingly, 2 phases can be recognised: in the 1st phase of gestation (0-18 d), both body and perirenal fat weights increased, while in the 2nd (19-26 d), despite the foetal growth, body and perirenal fat weight remained practically unchanged. These data agree with those reported by Parigi-Bini *et al.* (1990), where the total energy balance (EB) of does during pregnancy was positive (+2.41 MJ) and resulted in protein retention and body storage. In particular, their study revealed an initial phase (first 3 wk of pregnancy) with positive EB (+3.36 MJ) and a final phase with negative EB (–0.95 MJ) and intensive catabolism. In does fed *ad libitum*, Pascual *et al.* (2002a) found an increase of perirenal fat thickness until the 28th day of gestation (+1.8 mm) and a decrease in the last 3 d (–3.8 mm). In our study, we chose not to manipulate the does during the last 3-4 d of pregnancy, to avoid any interference with the welfare of rabbits close to parturition. Thus, the final evaluations were obtained at 26th d of gestation, although the feed restriction was continued until day 28.

The compensatory growth found in the R1 group after re-feeding coincides with previous data reported by other authors in non-pregnant rabbits fed *ad libitum* following a variable period of feed restriction (Pascual *et al.*, 2002b; Rommers *et al.*, 2004a; Tumova *et al.*, 2004), as well as in other mammals (Heyer and Lebret, 2007). However, contrary to the control group, body and perirenal fat weight of the R1 group did not increase during pregnancy, indicating an alteration of pregnancy-associated energy homeostasis with poor fat reserves stored for lactation. In the R2 group, there was no compensatory growth, probably because these rabbits did not have the possibility of restoring their fat deposits, as the full feeding corresponded to the period of late pregnancy characterised by increased energy demands. In the R3 group, the re-feeding may have occurred in the *post-partum* period, but this was not evaluated in our experiment.

The restricted groups did not lose body weight during pregnancy, but showed reduction of PFW (R2 and R3 groups) and/or BCS (R1 and R2 groups). Other authors reported high body weight loss during pregnancy, but their experimental protocols included more severe and/or more long-lasting dietary restrictions, such as 20 g/d (Matsuoka *et al.*, 2009) or 13 d of restriction (Cappon *et al.*, 2005). Nafeaa *et al.* (2011) found no decrease in body weight in pregnant does subjected to restriction (111 g/d) for the 1st half of pregnancy, but significant losses with feed reduction during the 2nd half of gestation. Moreover, especially during pregnancy, body weight change does not represent an exhaustive and reliable parameter for assessing body condition of females. In fact, the weight gain due to the growth of foetuses can mask the real body composition. The use of non-invasive techniques, namely perirenal fat weight and BCS, allowed a more accurate estimation of the body condition of pregnant rabbits. Indeed, our findings confirm the lack of any relationship between body weight and BCS as reported by other authors (Dal Bosco *et al.*, 2003; Cardinali *et al.*, 2008). Thus, the changes of perirenal fat and the reduction of BCS suggest that even a moderate undernutrition, especially in middle and late gestation, can result in inadequate stored reserves that may compromise health status, welfare and future reproductive performance of these females (Pascual *et al.*, 2013).

Productive performance

The effects of feed restriction on productive performance were associated with the gestation period in which the privation occurred: feed restriction in early pregnancy did not cause significant differences in productivity, while a restriction in the last third of pregnancy, a critical period for energy homeostasis, induced a reduction of productive performance. Manal *et al.* (2010) found that restriction of pregnant rabbit does for the first 15 or 20 d of pregnancy increased litter weight at weaning, while Nafeaa *et al.* (2011) did not observe any influence on litter size at birth and maternal body weights. Our results showed no changes in the litter size of R1 group, but lower milk yield, BCS, and fat stores which, taken together, indicate a poor body condition also in does subjected to feed restriction for the first 10 d of pregnancy. Possible explanations for these differences are the limited number of replicates and different nutritional protocols. Moreover, while the body condition of R1 rabbits at the end of gestation may have no immediate effect on productive performance, it can nonetheless hamper subsequent pregnancies. For this reason, dietary restriction during pregnancy is not recommended as a nutritional strategy for long-term improvement of performance and for animal welfare, although it would be interesting to conduct further studies that (i) employ *ad libitum* re-feeding instead of a rationed one as adopted here; (ii) evaluate several production cycles; and/or (iii) examine susceptibility to adult diseases. Previous studies have reported that markedly restricted feed intake (20 g/d) resulted in embryo-foetal death, probably due to progesterone reduction, and lower foetal body weight (Matsuoka *et al.*, 2009 and 2012). In our study, the non-pregnant rabbits were excluded 10 d after AI and no caesarean sections or ultrasound examinations were performed. Thus, our experimental protocol did not allow us to evaluate whether the level of feed during early gestation affected implantation, and further studies are required to assess the effects of energy restriction on embryo survival around implantation and/or abortion, including the evaluation of hormones essential in maintaining pregnancy, such as progesterone.

In our study, there was no case of malformations. Clark *et al.* (1986) reported an increase in the number of foetuses with malformation, but feed restriction was much more severe (15 g/d). Furthermore, contrary to results reported applying severe restriction (Matsuoka *et al.*, 2006), there were no differences in the duration of rabbit pregnancy.

Milk production increased until the last day of observation (18 d after kindling) and the resulting curve has been described previously by several authors (Maertens *et al.*, 2006). However, the nutritional level during pregnancy and body condition at kindling influenced milk production. Indeed, does from restricted groups produced a smaller amount of milk, probably because they did not have adequate reserves stored during gestation. Milk intake affects thermogenesis and immune protection of the newborn (Hill, 1992; Maertens *et al.*, 2006). So, we hypothesise that an inadequate milk intake can influence litter survival and may partially explain the high pre-weaning mortality of restricted groups. Furthermore, early undernutrition can have long-term effects, compromising the growth of young rabbits with negative consequences from the productive and reproductive viewpoint (Brecchia *et al.*, 2009; Pascual *et al.*, 2013). Finally, the productive parameters confirmed the poor body condition and long-term consequences of all rabbits subjected to feed restriction.

CONCLUSION

Body and fat weight gain during pregnancy ensure good productive performance of the rabbit doe. Feed restriction during mid and late stages of pregnancy induced loss of fat reserves, but even a feed restriction in the first period of pregnancy adversely affected rabbit doe body condition, partly explaining long-term consequences on both mother and offspring. On the other hand, our study confirms that the rabbit is a suitable model to study energy homeostasis and effects of undernutrition during pregnancy.

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