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Original article

Effects of simultaneous gestation and lactation in rabbit does on muscular characteristics of the youngs

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Summary — The aim of the experiment was to determine the influence of concurrent gestation and lactation in rabbit does on the post-natal growth and muscular characteristics of the progeny. Myosin heavy chain (MHC) isoform proportion, myofibrillar protein content and size of the myofibres were determined on day 29 or day 70 in the *semitendinosus* muscle of young rabbits born from either simultaneously pregnant and lactating does (PL group) or from only pregnant does (P group). There were no significant differences in the weight of the young rabbits of the two groups throughout the post-natal period, despite a non-significant reduction of birth weight by 9% in the PL group. On day 29, the proportion of perinatal MHC was higher (5.8% vs 2.3%) and that of the type-II isoforms was lower (91.5% vs 95.0%) in the PL group than in the P group ($P < 0.01$). The simultaneous gestation and lactation affected the maturation of secondary fibres. On day 70, the proportion of the MHC isoforms was similar in the two groups. These results suggest that concurrent gestation and lactation delayed the myofibrillar maturation rate.

rabbit / muscle fibre / lactation / gestation / post-natal growth

Résumé — Effects de la superposition de la gestation et de la lactation chez la lapine sur la croissance postnatale et les caractéristiques musculaires de la portée. L'objet de cette expérience était de déterminer l'influence d'une gestation et d'une lactation simultanées chez la lapine sur la croissance postnatale et les caractéristiques musculaires de la portée. À 29 et à 70 jours, la proportion des isoformes des chaînes lourdes de la myosine (MHC), la teneur en protéines myofribrillaires et la taille des fibres ont été déterminées dans le muscle *semitendinosus* des lapereaux nés de mères simultanément gestantes et allaitantes (groupe PL) ou de mères gestantes non allaitantes (groupe P). Les poids des animaux n'étaient pas très différents dans les deux groupes durant toute la période

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postnatale, malgré une réduction non significative de 9 % du poids à la naissance dans le groupe PL. À 29 jours, la proportion de MHC périnatale est plus élevée (5,8 vs 2.3 %) tandis que la proportion des isoformes de type II est plus faible (91.5 vs 95.0 %) dans le groupe PL, comparativement au groupe P. La concurrence entre la gestation et la lactation affecte la maturation des fibres de seconde génération. À 70 jours, la proportion des différentes isoformes est similaire dans les deux groupes. Ces résultats suggèrent que la concurrence entre la gestation et la lactation induit un retard dans la maturation des fibres musculaires.

lapin / fibre musculaire / lactation / gestation / croissance postnatale

INTRODUCTION

The female rabbit can be fertilized shortly after parturition and be simultaneously pregnant and lactating. But voluntary feed intake of primiparous does is insufficient to supply all the nutritional requirements for maternal tissue growth, foetal development and milk production (Maertens and De Groote, 1988; Fortun-Lamothe and Lebas, 1995). Therefore, energy balance of simultaneously pregnant and lactating does is highly negative (Parigi-Bini et al, 1991; Fortun and Lebas, 1994). This nutritional deficit induces a competition between uterus and mammary gland for nutrient supply (Fortun et al, 1994). Preliminary studies have shown that the foetal weight (observed on day 28 of gestation) is lower in lactating than in non-lactating does (–19.6%, Fortun et al, 1993), suggesting that foetal development is impaired by simultaneous pregnancy and lactation. However, effect of this lower foetal growth on post-natal development and muscular characteristics of the youngs is unknown.

Skeletal muscles consist mainly of muscular fibres differing in their biochemical and physiological characteristics. At a molecular level, myofibre types are related to the content in myosin heavy chains (MHCs) (Billeter et al, 1981). In rabbit skeletal muscles, two developmental (embryonic and perinatal) and four adult (I, IIa, IIb and IIx) MHCs isoforms have been identified (Aigner et al, 1993; Janmot and d'Albis, 1994). During foetal and early post-natal periods, expression of developmental isoforms is gradually suppressed while adult isoform expression is enhanced (rabbit: d'Albis et al, 1991; rat: Schiaffino et al, 1989; La Framboise et al, 1991). Perinatal MHC disappears between 28 and 35 days in rabbit limb muscle (Gondret et al, 1996). The proportion of the developmental and adult isoforms in rabbit fast limb muscle at 29 days of age can thus be used as a marker of muscle maturity. The aim of this work was to study the effects of simultaneous gestation and lactation in rabbit does on the post-natal growth of the youngs and their muscular characteristics at weaning (29 days) and commercial slaughter stage (70 days).

MATERIALS AND METHODS

Animals

Eight 24-week-old Californian × New Zealand rabbit does were assigned at their first parturition to one of the two experimental groups according to their litter size and body weight. In the first group, females ($n = 4$) were mated within 24 h after their first parturition, so that a second pregnancy occurred concurrently with lactation (pregnant lactating does, PL). The young rabbits born from the first pregnancy were weaned on day 28 of lactation. Therefore, the females were no more lactating and only pregnant during the last days of the second gestation (day 28 to day 31). The young rabbits born from the second pregnancy were used to study the muscle development (PL group). In the second group, the females ($n = 4$) were not remated after the first parturition (pregnant non lactating does, P) and the young rabbits of this pregnancy were used

(P group) to study the muscle development. The first parturition was chosen as control.

In the two groups, litters were equalized at eight young rabbits per female. Litter size before equalization is given in table I. In the two groups, the suckling rabbits were weaned on day 28 of lactation. The animals (does and weaned rabbits) had free access to water and to a commercial diet (17.5% crude protein, 2 330 kcal digestible energy per kilogram of feed). They were under controlled light/dark cycle (16/8 h). The does were caged individually whereas the growing rabbits were reared collectively after weaning.

Growth performance and muscle sampling

Only female youngs were studied. The youngs were weighed individually every week from birth (n = 16 in each group) to slaughter (n = 11 in each group). Youngs were slaughtered on day 29 (day postweaning) or day 70 (commercial slaughter age). Five animals from each group (one or two per litter) were slaughtered at each stage (five out of 16 on day 29 and five out of 11 on day 70), by electric stunning and exsanguination. In each group, they were chosen so that their weight at slaugther was representative of the weight of their littermates (mean and standard deviation). The white portion of the *semitendinosus* muscle was removed and frozen in isopentane cooled with liquid nitrogen. To take into account the heterogeneity of fibre type distribution, the whole transverse section of the white portion of the muscle was used for all further analyses. The muscles were divided into two parts: one for biochemical analyses and the other for histological examinations. *Semitendinosus* muscle was chosen because fast muscles have been generally thought to be more susceptible to nutritional influences (Dwyer and Stickland, 1992).

Myosin preparation

Frozen muscles were cut on ice into small pieces and washed with a solution of 20 mM NaCl, 3.4 mM PO_4H_2Na, 1.6 mM PO_4HNa_2, 1 mM EGTA pH 7. After centrifugation at 12 000 g (10 min at 4 °C), myosin was extracted from the pellet with three volumes of 100 mM sodium pyrophosphate, 5 mM EGTA, 1 mM dithiothreitol. The mixture was shaken during 30 min in ice and then centrifugated at 12 000 g for 10 min at 4 °C. The supernatant was mixed with glycerol at a final concentration of 50% (v/v) and stored at −20 °C until further analysis (d'Albis et al, 1979).

Electrophoresis of myosin heavy chains (MHC) isoforms

Electrophoresis was performed according to the method described by Talmadge and Roy (1993) and modified by Janmot and d'Albis (1994). The entire gel unit was placed in a styrofoam box containing ice to maintain the temperature below 10 °C during the 28 h run. Gels were stained with Coomassie Blue R-250. Embryonic- and IIa-MHCs could not be separated by this method because they migrated with the same mobility (Janmot and d'Albis, 1994). However, using immunocytochemical techniques, we have previously shown that embryonic MHC disappears in rabbit hindlimb muscles before 21 days (Gondret et al, 1996). Therefore, the band corresponding to both MHC-IIa and MHC-embryonic in the electrophoretic pattern, is actually IIa MHC at 29 and 70 days of age.

Quantification of the proportions of the different isoforms was obtained by using a densitometer equipped with an integrator (LKB 2202 Ultroscan densitometer).

Cytochemical analysis

For immunocytochemistry, cryostat serial cross-sections (10 μm) were reacted with a monoclonal antibody specific to rabbit perinatal MHC isoform (Novocastra, France). Specificity of this antibody has been demonstrated in a previous study (Gondret et al, 1996). After fixation in acetone, sections were rinsed in a 10 mM Na-K-Phosphate Buffer Solution (PBS) (pH 7.4), containing 137 mM NaCl and 2.7 mM KCl. They were then incubated overnight in a humid chamber at 4 °C with the antibody diluted ten fold. Specific antibody binding was revealed by the avidin biotin peroxidase technique (Vectastain ABC kit, Vector Laboratoris, Burlingame, CA). Proportion of fibres which stained positively with the anti-perinatal antibody was determined using 1 000 fibres in each sample.

For actomyosin ATPase cytochemistry, the remaining serial cross-sections (10 μm) were stained for actomyosin ATPase after preincubation at pH 4.3 (Brooke and Kaiser, 1970). Myofibres were classified in type I, IIA and IIB + IIX, and fibre type proportion was determined. Additional serial sections were reacted for succinate dehydrogenase (SDH) activity (Nachlas et al, 1957) in order to investigate the oxidative metabolism of the fibres. Percentages and mean cross-sectional areas of each type of fibre were determined by using a projection microscope (Visopan Reichert) and a programmable planimeter (Kontron, AMO 3).

Biochemical analysis

Muscle myofibrillar protein content was determined by the Coomassie blue (G250, Merck) binding assay of Bradford (1976), using bovine serum albumin as a standard.

Statistical analysis

Data are presented as means (± SEM) for each group. Influence of treatment on the proportion of runt animals (birth weight < 40 g) was tested by CHI2 analysis. Analyses of variance were performed with treatment as main effect (SAS-Package, 1990). Effect of weight at birth or weight at slaughter age on the proportion of the various isoforms was tested by analysis of variance.

Differences between P and PL groups were considered significant at $P < 0,05$.

RESULTS

Growth performance

Weight of the does at mating and parturition, litter size and birth weight of the litters and of the youngs in the two groups are given in table I. None of the traits differed significantly between the two groups.

Body weight curves of the young rabbits of the two groups from birth to 70 days of age are shown in figure 1. Birth weight was 9% lower in the PL group (49.86 ± 2.94 g) than in the P group (54.73 ± 3.33 g). How-

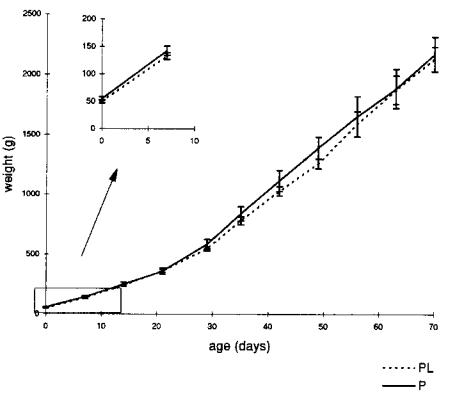

Fig 1. Post-natal growth performance of young female rabbits born from simultaneously pregnant and lactating does (PL group) or from pregnant non-lactating does (P group).

Table I. Traits of does and youngs of PL group and P group.

	PL group	*P group*
Weight at mating (g)	3 565 ± 74	3 710 ± 287
Weight at parturition (g)	3 493 ± 83	3 510 ± 319
Litter size before equalization	9.1 ± 0.9	9.2 ± 1.5
after equalization	8	8
Litter weight (g)	420 ± 30	433 ± 42
Birth weight of the youngs (g)	49.8 ± 2.9	54.7 ± 3.3

None of the traits differed significantly ($P < 0.05$) between the two groups.

ever, this difference was not significant ($P = 0.2$). Proportion of runt animals (birth weight < 40 g) was not influenced by treatment (22% and 26% in PL and P groups, respectively, $P = 0.7$). Post-natal growth performance was not significantly different between PL and P groups. At 29 days of age or 70 days of age, the live weight of the slaughtered animals (555 g and 560 g at day 29, and 2 128 g and 2 165 g at day 70, in groups PL and P, respectively) were representative of the weight of their littermates (545 g and 583 g at day 29, and 2 132 g and 2 171 g at day 70, in groups PL and P, respectively). The weights at the different slaughter ages were not affected by the animal birth weight ($P = 0.9$).

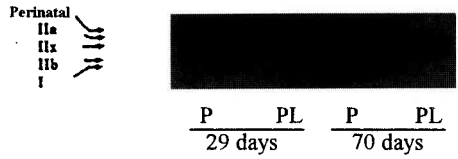

Fig 2. Characterization of the different MHC isoforms by SDS-Page at day 29 or day 70 in the white portion of the *semitendinosus* muscle of young female rabbits born from simultaneously pregnant and lactating does (PL group) or from pregnant non-lactating does (P group).

Proportion of the different MHC isoforms

At day 29, five MHC isoforms could be identified on the gels (fig 2). The electrophoretic mobilities of the isoforms increased in the order: perinatal, IIa, IIx, IIb and I. The major difference between the two groups was observed for the perinatal MHC isoform content, which was significantly higher in the PL than in the P group (5.8% of the total isoform content vs 2.3%, respectively, $P = 0.0006$, table II). Type II isoform content (ie, IIa + IIb + IIx) was lower in the PL than in the P group (91.5% vs 95.0%, $P = 0.01$). The proportion of type I isoform was not affected by treatment. At day 70, the perinatal isoform was no longer observed and the proportion of the different adult isoforms did not differ significantly between the two groups. Proportions of the various isoforms were not influenced by animal liveweight at birth or slaughter.

Fibre characteristics

After preincubation at pH 4.3, three types of fibres could be distinguished on the basis

Table II. Proportion of the various MHC isoforms in the *semitendinosus* muscle (white portion) of young rabbits born from simultaneously pregnant and lactating does (PL group) or from pregnant non-lactating does (P group).

MHC isoforms	*29 days*			*70 days*	
	PL group (n = 5)		*P group* (n = 5)	*PL group* (n = 4)	*P group* (n = 5)
Perinatal	5.8 ± 0.6	***	2.3 ± 0.4	0.0 ± 0.0	0.0 ± 0.0
IIa	8.1 ± 2.1		8.5 ± 0.7	11.5 ± 1.5	7.3 ± 2.0
IIx	49.4 ± 2.2		50.3 ± 1.9	49.5 ± 7.5	52.2 ± 2.6
IIb	34.0 ± 4.7		36.1 ± 2.6	33.0 ± 8.0	37.0 ± 2.3
I	2.7 ± 1.1		2.6 ± 0.6	6.0 ± 2.0	3.5 ± 1.6
Type II total	91.5 ± 1.6	**	95.0 ± 0.9	94.0 ± 2.0	96.5 ± 0.6

** $P < 0.01$ *** $P < 0.001$

Table III. Biochemical and histomorphological characteristics of the *semitendinosus* muscle (white portion) of young rabbits born from simultaneously pregnant and lactating does (PL group) or from pregnant non-lactating does (P group).

Variables	*29 days*		*70 days*	
	PL group (n = 5)	*P group* (n = 5)	*PL group* (n = 4)	*P group* (n = 5)
Fibre size (μm^2)				
I	475 ± 59	420 ± 47	1 590 ± 356	1 468 ± 312
IIA	407 ± 25	397 ± 29	1 445 ± 307	1 425 ± 151
IIB	544 ± 37	534 ± 63	1 759 ± 236	1 636 ± 111
Fibre type (%)				
I (deep area)	8 ± 2.1	7 ± 2.3	16 ± 5.1	13 ± 3.2
(superficial area)	1 ± 0.7	2 ± 0.8	5 ± 1.3	4 ± 1.4
IIA (deep area)	12 ± 2.7	14 ± 1.6	22 ± 1.1	16 ± 1.2
(superficial area)	5 ± 1.2	5 ± 0.8	17 ± 0.8	15 ± 0.6
IIB (deep area)	80 ± 2.4	79 ± 1.5	62 ± 0.7	71 ± 1.3
(superficial area)	94 ± 3.6	93 ± 2.3	78 ± 1.2	81 ± 1.8
Myofibrillar proteins (mg/g muscle)	5.2 ± 0.8	6.3 ± 0.8	6.6 ± 0.2	6.7 ± 1.1

of their different staining intensity: type I (high staining intensity), type IIB + IIX (intermediate staining intensity) and type IIA fibres (low staining intensity). Repartition of the fibres was heterogeneous, with a continuum between two portions in the muscle. The deep medial portion contained more type I fibres (8% and 15% of type I at day 29 and day 70, respectively) than the superficial area (1% and 4% of type I at day 29 and day 70, respectively, table III). At day 70, type IIB + IIX fibres exhibited a larger size (1 691 μm^2) than type I fibres (1 522 μm^2) and type IIA fibres (1 434 μm^2). There was no significant difference between the two groups for the size of the different fibre types at day 29 and day 70 (table III). Perinatal MHC isoform was expressed in a subpopulation of the type II fibres in the two groups (fig 3). At day 29, the proportion of fibres positively stained by the anti-perinatal antibody was two-fold higher in the PL than in the P group (10% vs 4.8%, $P = 0.04$).

Protein content

The myofibrillar protein content did not differ significantly between the two groups at days 29 and 70 (table III).

DISCUSSION

The present results suggest that concurrent pregnancy and lactation delayed the maturation of the muscular fibres of the young rabbits.

Fortun et al (1993) have previously shown that foetal growth was reduced in lactating compared to non-lactating does. On day 28 of gestation (3 days before parturition), foetal weight was 19.6% lower in simultaneously pregnant and lactating does than in pregnant does. In the present study, the difference in the weight of the youngs of the two groups observed at birth was lower (–9%) and was not significant. During the last 4 days of pregnancy (28 to 31), when

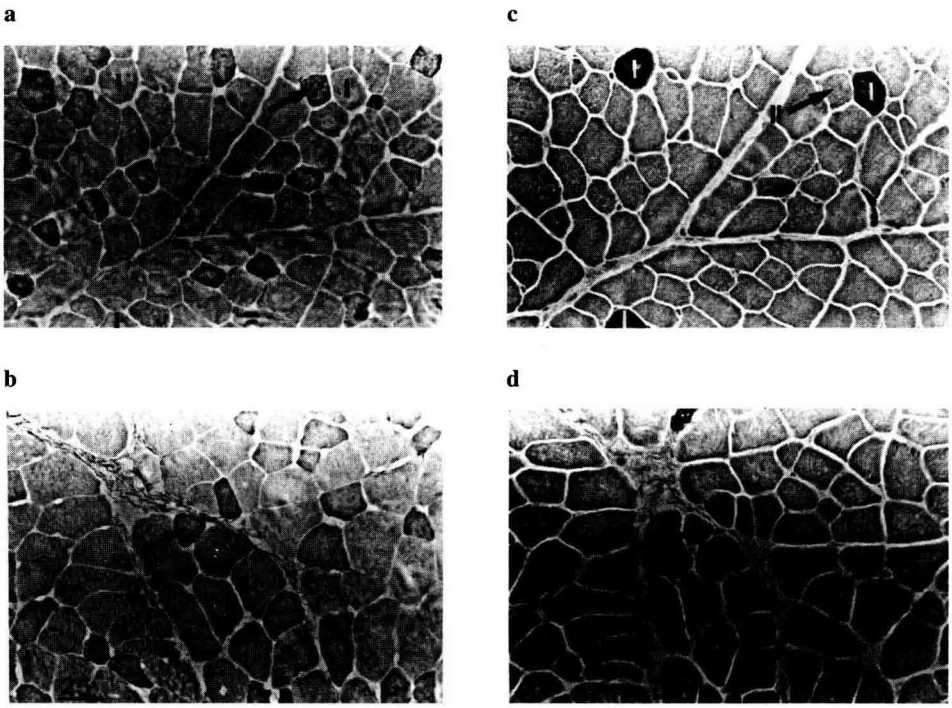

Fig 3. Immunocytochemical and histochemical analysis of transverse serial sections in the white portion of the *semitendinosus* muscle, after incubation with an antibody raised against perinatal MHC (a: PL group, b: P group) or after preincubation at pH 4.3 (c: PL group, d: P group) at the age of 29 days. Scale bar = 25 μm. $n = 5$ in each group.

foetal growth is maximal, PL does were no more lactating (weaning occurred on day 28) and probably had a higher feed intake than P does, as previously observed by Fortun (1994). Therefore, a catch-up growth of foetuses from PL does at the end of pregnancy may have occurred and could explain the close birth weight observed in the two groups, in spite of a lower foetal growth in PL group during the beginning of gestation. After birth, growth of the youngs born from does previously lactating or not lactating did not differ significantly.

At day 29, the present observations, combining electrophoresis and immunohistological techniques, show that perinatal MHC proportion was higher in muscle of the youngs born from simultaneously pregnant and lactating does than in the youngs from pregnant non-lactating does, thus suggesting a delay in the maturation of their myofibres. Acquisition of mature muscle phenotype is controlled by complex regulatory mechanisms, including nervous, hormonal and nutritional factors during foetal and postnatal periods (Vigneron et al, 1989, Ward and Stickland, 1993, Dwyer and Stickland, 1994).

During pregnancy, Fortun and Lebas (1994) have shown that energetic balance during the first 28 days of gestation is highly negative in does which are simultaneously pregnant and lactating (–11.78 MJ), whereas it is positive in pregnant non-lactating does

(+12.51 MJ). The nutritional deficit in simultaneously pregnant and lactating does induced a competition between uterus and mammary gland for nutrient supply and it seems likely that nutrient availability for the foetuses was impaired. Undernutrition during pregnancy is known to affect negatively the number of myofibres (Handel and Stickland, 1987; Ward and Stickland, 1991; Dwyer et al, 1993), affecting preferentially secondary fibres in guinea pig (Dwyer and Stickland, 1994; Dwyer et al, 1994).

Our data suggest that the transition from perinatal to type II myosins was affected by nutritional influences in utero, since type II MHC isoform proportion was lower in PL group than in P group. At birth, in rabbit fast hindlimb muscles, type II isoform is expressed exclusively in secondary generation of fibres (Gondret et al, 1996). Therefore, in our conditions, the simultaneous gestation and lactation affected the maturation of the secondary generation of fibres. In pig, Stickland (1995) notices that secondary fibres are more labile to nutritional influences in utero than primary generation. In the rabbit, the transition from perinatal to type I isoform mainly occurs in the primary generation of fibres before birth (Gondret et al, 1996). Therefore, in our experimental design, we are not allowed to conclude whether or not the maturation of the primary generation of fibres has been affected by simultaneous gestation and lactation.

High thyroid hormone levels inhibit the synthesis of perinatal myosin and activate adult fast myosin synthesis in developing rabbits (d'Albis et al, 1987) and rats (Butler-Browne et al, 1984). Thyroid hormones status is modulated by energy balance (Riis and Madsen, 1985; Symonds, 1995). Therefore, the deficiency in maternal energy intake during pregnancy in simultaneously pregnant and lactating does could contribute to low T4 levels in the foetuses, as shown in guinea-pigs (Dwyer and Stickland, 1992) and low plasma free T3 concentrations in the newborn, as noticed in sheep (Symonds, 1995) and could therefore explain the delay in the perinatal myosin disappearance observed in PL youngs.

Post-natal undernutrition has been shown to be detrimental to the optimal muscle maturation rate (guinea-pig: Ward and Stickland, 1993), by decreasing the plasma thyroid hormone levels in the youngs (rat: Cox et al, 1984; Jepson et al, 1988; piglet: Campion et al, 1986). Concurrent gestation and lactation decreases sharply (68%) the fat body reserves of the rabbit does (Fortun et al, 1993). This low lipid reserves could impair the milk production of the does during the ensuing lactation. Therefore, youngs born from pregnant and lactating does could have been undernourrished during the suckling period. However, this seems unlikely because no difference was observed between the growth rate of the two groups of youngs throughout the post-natal period.

At day 70, no difference was observed between the two groups about the adult isoform proportion and fibre type proportion in the white portion of *semitendinosus* muscle, suggesting that concurrent gestation and lactation did not alter definitively the myofibre type proportion of the progeny. This is in agreement with Nordby et al (1987), who have shown that maternal dietary restriction during pregnancy does not affect fibre type proportion in *semitendinosus* muscle of 55 kg BW lambs. In addition, early undernutrition during pregnancy does not alter fibre type proportion of *extensor digitorum longus* (EDL) in 20-week-old rats (Howells et al, 1979). Yambayamba and Price (1991) have also shown that feed restriction during post-natal period has no effect on the percentage of fibre types in cattle. However, when the degree of maternal restriction is very high, fibre type proportion in the progeny can be altered until adulthood in rats or pigs (Howells et al, 1978; Powell and Aberle, 1981; Bedi, 1982), with runt pigs exhibiting higher percentage of type I fibres

and lower percentage of type II fibres than normal birth weight littermates (Powell and Aberle, 1981). Therefore, in our experiment, nutrient deficiency induced by concurrent pregnancy and lactation might have been insufficient to induce changes in muscle fibre type proportion in 70-day-old rabbits.

Myofibrillar protein concentration and size of the different myofibres in *semitendinosus* muscle seemed to be unaffected by concurrent lactation and gestation. This is in accordance with the results of Pond et al (1990) in swine, where total protein content in a cross-section of the *longissimus* muscle is similar for progeny of adequately-fed dams, feed-restricted dams or protein-restricted dams. On the opposite, Howells et al (1978), as well as Bedi (1982), have shown that prenatal feed restriction alters fibre size of rat fast muscles. On the other hand, runt pigs are associated with larger muscle fibre diameter, when compared with normal birth weight littermates (Hegarty and Allen, 1978). In addition, level of nutrition during post-natal period can also affect fibre size. Fibre sizes are smaller in post-natal undernourrished guinea-pigs (Ward and Stickland, 1993) or rats (Tanaka et al, 1992). Therefore, in our experiment, the nutrient deficiency induced by concurrent pregnancy and lactation might have been insufficient to induce any change in muscle fibre cross-sectional areas.

CONCLUSION

The concurrence between gestation and lactation does not seem to influence the post-natal growth of the progeny, but delays the maturation rate of the muscular fibres. This effect is not permanent since it is no more observed at commercial slaughter age. The mechanisms that are implicated in the effect of simultaneous gestation and lactation remain to be clearly elucidated.

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