Effect of consanguinity and selection on the components of a productive index, in mice under close mating

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Abstract:

In order to examine the influence of inbreeding depression on some productive characteristics of the laboratory mouse, 871 records were reanalyzed, which were from 20 generations in a line with narrow inbred crossing with selection for a productive index (WOFW) comparing with a line without selection, with inbred crossing (n= 135). Inbreeding coefficients (F) were calculated for each generation. In all the components of the index (reproductive life, fertile postpartum estruses and litter size), the two lines were compared, in the 15 available generations of the non-selected one, by the least squares method, grouping every five generations. The selected one was analyzed in the 20 generations for intergenerational differences with the same method. Inbreeding depression was estimated in all generations with a linear regression of consanguinity (expressed in 10 %) in all components. A significant difference (*P*<0.01) was observed between lines in the variables analyzed. The fertile postpartum estruses of the selected line remained constant, there was a decrease of 0.331 in the non-selected one (*P*<0.01). The productive index remained stable (increased 0.071) in the selected one, in the non-selected one it decreased (0.39) until disappearing (G15). Inbreeding depression impacted the reproductive life of both, decreased 4.741 d in the selected one *vs* 7.718 d in the non-selected one (*P*<0.01). In the non-selected one, it affected mortality at weaning and

estrous cycle, the selection to the index counteracted that impact, probably due to the selection of genes that favor the gonadal development of mice.

Introduction

At present many genetically different mouse lines have been developed, which have particular research purposes. The inbred lines were the prototype of the genetically standardized lines, which allowed developing experiments eliminating the variability of genetic origin. Although genomics provides laboratories with the necessary tools to produce mice with the characteristics that research demands, when a characteristic has been fixed, a rigorous selection and directed mating process is needed to maintain the viability of the line, which usually leads to inbreeding depression[1,2].

The genetic basis of this phenomenon is related to three hypotheses, namely, partial dominance (greater expression of deleterious recessive alleles), overdominance (superiority of heterozygotes over both types of homozygotes) and epistasis (greater probability of genetic combinations favorable to heterozygotes)[3].

Breeders of purebred domestic animals use inbreeding to fix desirable genetic traits within a population or to try to eliminate deleterious traits, inbreeding depression can affect the economic income of breeders[4]. Studies in mice, by offering a greater number of generations in less time, help to understand inbreeding depression, in populations where it is sought to select some characteristic.

In the mouse, a 7.2 % reduction in litter size was observed for every 10 % increase in consanguinity, under consecutive mating of complete siblings without selection[2] and, with the same increase in consanguinity in crosses between half-siblings without selection, the decrease was 6.22 % in litter size[5].

Depression was less severe in lines under directed selection than in lines without selection[6], this was observed when selecting for litter size in mice, finding that the reduction in the reproductive ability was significantly lower in inbred lines under selection, compared to that of inbred lines without selection; this is explained because

thanks to selection, there is an increase in genes related to better reproductive ability, which counteracts the inbreeding depression that causes the reduction of this ability[7]. It has been seen that the behavior of an inbred line selected for litter size is similar to that of a non-inbred line, selected for the same trait. In one study, consanguinity allowed exceeding the limit of selection for large litter size, when in the selected line an inbred crossing was allowed[8].

The number of weaned offspring per female per week (WOFW) is a productive index that is measured during and at the end of the reproductive life in each pair of mice. It is used in the founding colonies of some laboratory animal companies[9,10]. Although it is recommended to select mice from families with higher WOFW to maintain laboratory lines, by narrow inbred crossing with fixed characteristics[11], in the literature there is little information on the effect of this selection in inbred mice on the variables included in it.

Therefore, the objective of this study was to evaluate the effect of inbreeding on the components of a productive index, in the animal model of laboratory mouse, during 20 generations of selection with narrow inbred crossing, as well as to evaluate whether the selection can be affected in its progress, by the effect of inbreeding depression, in the characteristics that constitute it.

Material and methods

The present work is a retrospective, cross-sectional, comparative and observational study. Eight hundred seventy-one records of a bioterium were reanalyzed, which were taken for five years in mice with continuous selection and narrow inbred cross (brother with sister), where there were five lines selected for a productive index: (WOFW) in 20 generations (n= 871). The data, collected between 1989-1994, had been analyzed with the aim of obtaining realized heritability, for the productive index, a detailed description can be seen in Tapia-Pérez[12].

For this study, a line of the same contemporary strain was added, which was from the same bioterium (n= 135), with narrow inbred crossing without selection until generation 15; after this generation the pairs ceased to be fertile.

The animals were housed in shoebox-type polycarbonate cages, which offer an area of 375 cm, with Cambridge-type stainless steel lid and Kraft-type rigid polyester filter; food was provided *ad libitum*, drinking water filtered by reverse osmosis acidified at a pH of 2.5. The air was filtered, and a temperature of 18 to 26 °C was maintained. The identification of the animals was individual, first, by means of notches in the ears, and the records by means of cards in each cage. These cards were then summarized in record folders called REA (Reproductive Efficiency Analysis), from which the WOFW index

was calculated every three generations, or when divergent lines were detected (this could occur in the fourth generation in each selected line), to obtain and select the subline with the highest average, which also had offspring of the third parturition, with at least two females and two males for breeding. It should be noted that those pairs who were sterile (no gestation was recorded), infertile (gestation was recorded, but not parturition) or who cannibalized their offspring had a WOFW value of zero, which was included to obtain the average since they are considered the result of inbreeding depression. As for the non-selected line, the management was similar; this line was the only one that remained active of the five that started at the same time of the selected ones, the other four were lost in the second generation. Reproductive management in both lines was under an intensive monogamous method, that is, a male with a female were placed in the same cage and remained together throughout their reproductive life (165 ± 3.6 d). Mating began when the animals reached sexual maturity (8-10 wk).

The pairs selected for reproduction were formed randomly, a female and a male full siblings, from the third parturition of their parents, both in the selection generation (3 or 4) and in the previous ones. An average of eight pairs per line was maintained in each generation.

Description of variables

The variables that were analyzed were:

RL: reproductive life, measured as the total days in reproduction.

FPPE: total number of fertile postpartum estruses in RL. A fertile postpartum estrus is considered when the female has a parturition in the first estrus, within 35 or less days from the previous one (since a gestation period of 21 d is assumed, with an implantation within 5 d, if this occurs out when the mother is still lactating a previous litter, it can occur in 14 d maximum, thus: 21 + 14 =35)[9].

OBOR: total number of offspring born in RL.

OWEA: total number of offspring weaned in RL.

OBPP: offspring born per parturition $= \dfrac{OBOR}{PARTURITIONS}$ (PARTURITIONS: number of total parturitions in RL).

OWPP: offspring weaned per parturition $= .\dfrac{OWEA}{PARTURITIONS}$

WOFW: (Productive Efficiency Index) is the number of weaned offspring per female per week $= \dfrac{OWEA}{RL} \times 7$.

Percentage of mortality at weaning $= \dfrac{OBPP-OWPP}{OBPP} \ X100$.

Statistical analysis

For the statistical analysis, the selected line corresponds to the set of the five lines with selection for WOFW divided into: line selected for 15 generations (S15G) n= 733, the same line selected in the 20 generations (S20G) n= 871 and non-selected line, which remained until generation 15 (NS15G) n= 135, since in this one, there were five pairs, of which only one reached the third parturition and the offspring were not enough to make the crosses.

The information of five generations in each line was grouped, for all the variables, so that the data analyzed at each level correspond to those of five successive generations. They were grouped in this way to observe the result of the selection in the fifth generation, because, as explained, the selection was made at least every three generations or when divergent lines were detected, which could occur in up to four generations. Level 1 contains the sum of generations from 1 to 5; level 2, from 6 to 10 and level 3, from 11 to 15 of S15G and NS15G, while level 4 only corresponds to S20G, in generations 16 to 20.

Normality tests of the variables mentioned were performed by the Kolmogorov-Smirnov method.

The general linear model used to compare S15G and NS15G was (Model 1):

$$Y_{ijk} = \mu + s_i + g_j + (sg)_{ij} + \varepsilon_{ijk}$$

Where
Y_{ijk} is the sum of five successive generations of pairs, for each quantitative variable;
s_i is the effect of the i-th selection group (i=1,2);
g_j is the effect of the generation grouped every five generations (j=1,2,3);
$(sg)_{ij}$ is the effect of the interaction between the selection group and the grouped generation;
ε_{ijk} the random error ($\varepsilon \sim N_{0,\sigma_\varepsilon^2}$).

The analysis model for S20G (Model 2) only included the effect of the grouped generation g_i, (i=1,2,3,4):

$$Y_{ij} = \mu + g_i + \varepsilon_{ij}$$

Where
Y_{ij} is the sum of 5 successive generations of pairs, for each quantitative variable, in the i-th generation;
ε_{ij} the random error ($\varepsilon \sim N_{0,\sigma_\varepsilon^2}$).

Both models were analyzed by the least squares method. The coefficient of consanguinity was calculated for each animal, with the Pedigree Viewer© Computer Program, developed by Brian Kinghorn[13], which uses the method developed by Wright (1922)[14].

The mean inbreeding depression ($\hat{\beta}_1$) and its standard error (s.e.), of WOFW were estimated by the least squares method with the coefficients of consanguinity (F_i) of each generation, in units of 10 % for lines S15 and NS15 (i= 1,2,3, ...,15) and S20 (i= 1,2,3, ..., 20), with the following simple linear regression model. (Model 3)

$$\hat{Y}_i = \widehat{\beta_0} + \widehat{\beta_1}F_i + e_i$$

Where

$\hat{Y}_i$ is the average of each component of the index in the i-th generation;

$\widehat{\beta_0}$ is the estimate of the intercept;

$\widehat{\beta_1}$ is the mean inbreeding depression, F_i is the coefficient of consanguinity (10 %);

e_i is the random error ($e_i \sim N_{\mu,\sigma_e^2}$).

Since the increase in inbreeding was considered in units of 10 %, inbreeding depressions were related to this measure, which was chosen to be able to compare the results of this study with other mouse articles where it is calculated in that way.

The models were analyzed with the statistical package, IBM SPSS Version 22[15], the percentages of mortality at weaning, of S15G and NS15G, in each of the three generations grouped, were analyzed by the Chi-square test, with the online MedCalc® program[16]. The *P* value ≤0.05 was considered as significant and *P*≤0.01 as highly significant.

Results

Linear models

Model 1

A highly significant effect of selection group (s_i) (*P*<0.01) was observed in all variables. Regarding the interaction (sg)$_{ij}$, in the variables FPPE, OBOR, OWEA and WOFW, it was highly significant (*P*<0.01), in RL and OWPP, the effect of the interaction was significant (*P*<0.05), which did not happen in the OBPP variable (*P*>0.05) (Table 1).

Table 1: Least squares means (M) and standard errors (SE) of the interaction $(sg)_{ij}$, in five grouped generations, for S15G and NS15G

LINE	GG	F(%)		FPPE	RL	OBOR	OWEA	OBPP	OWPP	WOFW
S15G[A]	1 - 5	50	M	1.74[a]	165.2[a]	20.35[a]	17.77[a]	4.77[a]	4.16[a]	0.66[a]
(n=733)			SE	1.58	3.52	8.16	7.65	1.59	0.54	0.029
	6 - 10	82.6	M	2.18[a]	129.5[b]	19.01[a]	16.09[a]	4.62[a]	3.92[a]	0.598[a]
			SE	1.62	3.44	10.33	10.29	2. 06	2.27	0.029
	11 - 15	93.9	M	2.1[a]	146.2[a]	21.06[a]	19.31[a]	5.01[a]	4.60[a]	0.687[a]
			SE	1.5	3.32	9.78	9.61	1.92	2.00	0.028
NS15G[B]	1 - 5	50	M	2.65[a]	146.7[a]	17.16[a]	13.63[a]	3.76[a]	2.96[a]	0.59[a]
(n=135)			SE	1.63	6.64	7.52	7.164	1.26	1.49	0.055
	6 - 10	82.6	M	1.32[b]	99.67[b]	7.76[b]	4.64[b]	3.04[a]	1.45[b]	0.12[b]
			SE	1.41	7.74	4.37	4.85	1.45	1.70	0.064
	11 -15	93.9	M	0.3[c]	99.75[b]	7.85[b]	6.15[b]	3.87[a]	2.88[a]	0.20[b]
			SE	0.66	8.36	5.26	5.59	1.57	2.10	0.069
P(SG)				<0.01	0.047	<0.01	0.01	0.482	0.048	<0.01

GG= grouped generations. F= consanguinity obtained in 5 generations. FPPE= number of fertile postpartum estruses. RL= reproductive life of the pair in days. OBOR= total number of offspring born in RL. OWEA= total number of offspring weaned in RL. OBPP= offspring born per parturition. OWPP= weaned offspring per parturition. WOFW= number of weaned offspring per female per week.

[A,B] Different literals denote highly significant differences between the selection groups s_i ($P<0.01$).

P(SG) is the significance calculated by the model,

[abc] Different literals denote significant intergenerational differences ($P<0.05$), within line.

The means of the FPPEs of S15G increased 0.44 estruses and remained ($P>0.05$), while the means of NS15G decreased 2.4 estruses on average, from 1 to 5 until generations 11 to 15 ($P<0.05$) (Table 1 and Figure 1). Reproductive life (RL) decreased in S15G, almost 36 d ($P<0.05$) in generations 6 to 10, then recovered, although not at the level of the first five generations, while in NS15G it remained 47 d lower than in the first five generations ($P<0.05$). Both the number of offspring born and weaned, in the total reproductive life of the pairs, the lowest values were observed in generations 6 to 10 in both lines; however, only NS15G showed significant differences ($P<0.05$) with a decrease of 9.4 and 9 offspring, respectively. Both OBPP and OWPP were obtained as an average of all parturitions in the reproductive life of the female, grouped every five generations and were lower in NS15G, the lowest peak was observed between generations 6 to 10 in both, but it was only significant in NS15G in OWPP with a decrease of 0.7 weaned offspring ($P<0.05$) (Table 1).

Figure 1: Means and standard deviations of the number of fertile postpartum estruses (FPPE) with consanguinity grouped every five generations (1 to 5, 6 to 10 and 11 to 15)
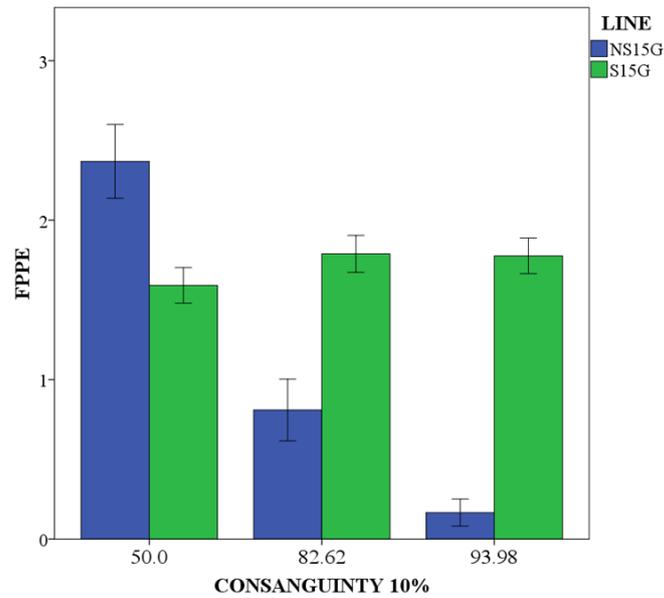
S15G and NS15G are the lines with selection and without selection for WOFW in the 15 generations of the latter.

The index (WOFW) remained stable through all accumulated generations (P>0.05) in S15G, while NS15G has an abrupt drop from generations 1-5 to 6-10 (-0.47 offspring) (P<0.05), with a slight recovery in the following five grouped generations (0.08 offspring) (P<0.05); then it is lost due to high mortality (Table 1 and Figure 2).

Figure 2: Means and standard deviations of the number of weaned offspring per female per week (productive efficiency index) (WOFW) with consanguinity grouped every five generations (1 to 5, 6 to 10 and 11 to 15)
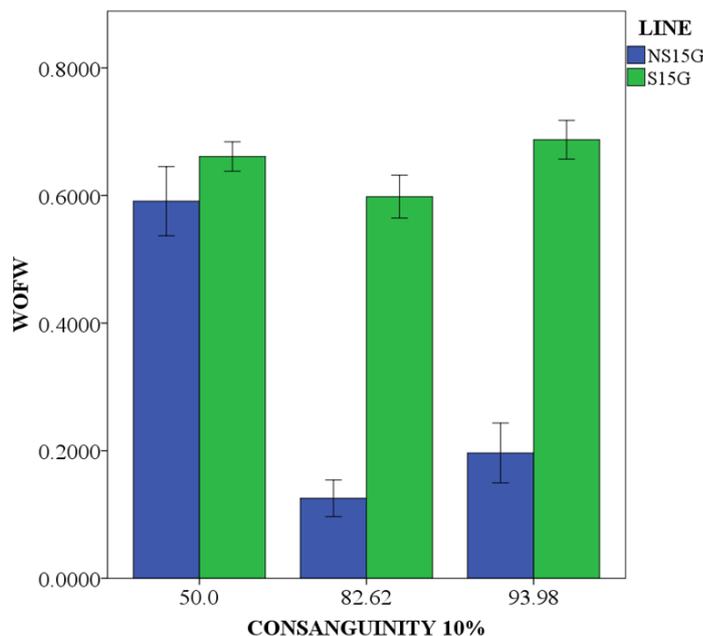
S15G and NS15G are the lines with selection and without selection for WOFW in the 15 generations of the latter.

Model 2

When S20G was analyzed, the lowest peak was observed in generations 6 to 10 ($P<0.05$), in almost all components, while FPPE and the WOFW index showed no significant intergenerational changes ($P>0. 05$) (Table 2).

Table 2: Least square means (M) and standard errors (SE) of five generations grouped, for S20G.

GG	F(%)	STA	FPPE	RL	OBOR	OWEA	OBPP	OWPP	WOFW
1 to 5	50	M	1.59[a]	165.2[a]	18.64[a]	16.29[a]	4.77[a]	4.17[a]	0.616[a]
		SE	0.12	3.58	0.81	0.76	0.14	0.14	0.031
6 to 10	82.6	M	1.79[a]	130.0[b]	15.26[b]	12.92[b]	4.63[a]	3.92[b]	0.598[a]
		SE	0.12	3.49	0.78	0.74	0.14	0.15	0.030
11 to 15	93.9	M	1.78[a]	146.7[c]	17.64[ab]	16.17[a]	5.01[a]	4.59[a]	0.687[a]
		SE	0.11	3.38	0.76	0.71	0.13	0.14	0.029
16 to 20	97.4	M	1.80[a]	133.9[bc]	17.26[ab]	15.17[ab]	5.18[b]	4.49[ab]	0.675[a]
		SE	0.11	3.39	0.76	0.72	0.14	0.14	0.029

GG= grouped generations. F= consanguinity grouped into 5 generations. STA= statistic. FPPE= number of fertile postpartum estruses. RL= reproductive life of the pair in days. OBOR= total number of offspring born. OWEA= total number of offspring weaned in RL. OBPP= offspring born per parturition. OWPP= offspring weaned per parturition. WOFW= number of weaned offspring per female per week.
[abc] Different literals denote significant intergenerational differences ($P<0.05$).

Model 3. Inbreeding depression

There was a highly significant effect ($P<0.01$) of inbreeding depression in S15G, in RL, OBPP and OWPP, while in OBOR, OWEA, FPPE and WOFW it was not significant ($P>0.05$); in NS15G, the characteristics FPPE, RL, OBOR, OWEA and WOFW showed a highly significant effect ($P<0.01$) of inbreeding depression, however, in OBPP and OWPP, it was not significant ($P>0.05$) (Table 3).

Table 3: Mean non-standardized regression coefficients ($\hat{\beta}_1$) and their standard error (SE), of the WOFW components and of the index itself, in NS15G, S15G and S20G, on the coefficient of consanguinity

Line	Statistic	FPPE	RL	OBOR	OWEA	OBPP	OWPP	WOFW
S15G	$\widehat{\beta_1}$	0.052	**4.741**	-0.454	-0.332	**-0.466**	**-0.578**	-0.001
(n=733)	SE	0.030	1.276	0.256	0.256	0.084	0.086	0.007
NS15G	$\widehat{\beta_1}$	**0.331**	**7.718**	**-1.705**	**-1.325**	0.028	-0.010	**-0.062**
(n=135)	SE	0.066	2.507	0.341	0.326	0.087	0.109	0.015
S20G	$\widehat{\beta_1}$	0.047	**-4.76**	-0.361	-0.268	0.02	0.026	-0.001
(n=871)	SE	0.026	1.09	0.213	0.210	0.036	0.036	0.007

S15G= line with 15 generations of selection. NS15= line without selection for 15 generations. S20G= same line with selection for 20 generations. FPPE: number of fertile postpartum estruses. RL= reproductive life in days. OBOR= offspring born in the total reproductive life. OWEA= offspring weaned in the total reproductive life. OBPP= offspring born per parturition. OWPP= offspring weaned per parturition. WOFW= number of weaned offspring per female per week.
Regression coefficients in bold were highly significant (*P*<0.01).

Reproductive life decreased in both lines for every 10 % of consanguinity, NS15G 7.718 days *vs.* 4.741 in S15G (*P*<0.01). In OBOR and OWEA, there was an effect of inbreeding depression only in NS15G (-1.705 and -1.325 offspring, respectively) (*P*<0.01). OBPP and OWPP were obtained as an average of the parturitions in the RL of each pair, in these variables, the inbreeding depression only affected S15G (-0.466 and -0.578 offspring, respectively) (*P*<0.01), while in NS15G there was an apparent stability (*P*>0.05), because the average number of parturitions in the accumulated generations was decreasing (4.2, 1.7 and 1.1), in the accumulated generations 1 to 5, 6 to 10 and 11 to 15 respectively, while in the selected one, they remained almost unchanged (3.9, 3.8 and 3.6). The WOFW index did not show inbreeding depression in S15G (*P*>0.05), the opposite occurred in NS15G (*P*<0.01). On the other hand, S20G showed highly significant inbreeding depression of -4.76 d in RL for every 10 % increase in consanguinity (*P*<0.01) (Table 3).

Mortality at weaning

The percentage of mortality per parturition at weaning, with respect to OBPP, had a similar behavior in both lines, with a maximum peak in generations 6 to 10, however, the non-selected line maintained a higher mortality than the selected one (52.30 %), having a difference with the selected one of 36.8 ($P<0.01$) (Figure 3). Survival per parturition (100 - % mortality per parturition) then declines, in the generations from 6 to 10, 31 % in the non-selected line (78.47 - 47.7 %) and 2.37 % in the selected line (87.22 - 84.85 %), remaining higher in the line with selection.

Figure 3: Mortality per parturition at weaning, in percentage with respect to OBPP, with consanguinity grouped into 5 generations
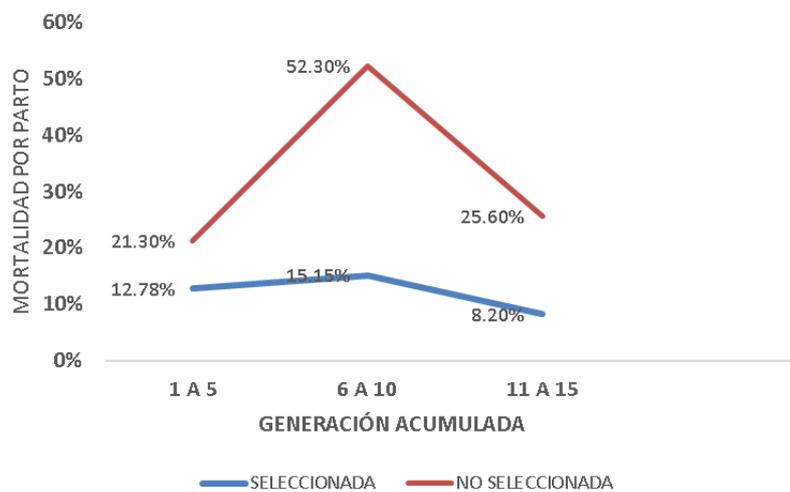
S15G and NS15G are the lines with selection and without selection for WOFW in the 15 generations of the latter.

Discussion

In the literature, there are few selection papers on long-term fertility and its effect on inbreeding depression in mice; in a study of selection of litter size at the first parturition that began in 1972, avoiding crosses between complete siblings, half-siblings or cousins, after 124 generations of selection, a consanguinity of 0.64 was found in one of its lines, which led it to greater inbreeding depression (-0.39), with a lower number of live offspring at the first parturition, for every 10 % of consanguinity[17]. The results of the present work coincide with that, when the average of the offspring born alive per parturition (OBPP) was obtained in the line with selection, the effect of inbreeding depression was -0.466, a little higher than that, because in that work only the first parturition was measured. The number of offspring born per parturition, in the NS15G group, showed a non-significant effect of consanguinity ($P>0.05$) (Table 3), which

seemed contrary to what was expected; the explanation is that the number of parturitions in the reproductive life of the pairs was decreasing as the generations increased and when averaging the size of the litter at parturition and weaning (of the whole RL of each pair) with these, it seems that it would have remained constant ($\hat{\beta}_1 = 0.028$). Another difference is that the consanguinity in that study is lower, although the number of selection generations is 124, during that time (1972 to 2007), there were several changes in the direction of selection in that work, but it was tried to avoid inbred crosses[17]. No work with selection for litter size of the entire reproductive life with inbred cross was found in the literature, however, in a study with selection for an index combining litter size with birth weight, but with open crosses (not inbred) for 150 generations, litter sizes of 17.6 offspring born and 20.2 offspring on average[18] in the reproductive life of a pair were obtained, very similar to the average OBOR at the beginning of this study. The decrease in this average in the following generations in the present work is most likely due to inbreeding depression, which was -1.705 offspring for every 10 % of consanguinity ($P<0.01$) in the non-selected line. It should be noted that in the OBOR and OWEA characteristics, originally used to obtain the WOFW (in all the RL of each pair), there was a highly significant effect ($P<0.01$) of inbreeding depression in NS15G , which does not occur in S15G (Tables 1, 2 ,3). In that study, an increase in testosterone levels was observed in males, while in females there was an elevation of progesterone in one of its lines; these showed a higher number of oocytes per cycle, but a greater loss of embryos, and a decrease in reproductive life, compared to the line without selection. These results coincide with the present work since a decrease in reproductive life was also obtained in S1G and S20G (Tables 1, 2).

In the present study, it was revealed that the number of FPPE has a constant decrease over the generations studied in NS15G, with a decrease of 0.331 fertile postpartum estruses for every 10 % increase in consanguinity ($P<0.01$), compared to S15G which remains almost constant ($P>0.05$) (Table 3); this behavior is also observed in WOFW (the productive index), with a marked decrease in NS15G of generations 1 - 5 to 6 - 10, with a slight recovery in the last five; inbreeding depression was -0.062 ($P<0.01$) weaned offspring per female per week for every 10 % increase in consanguinity, *vs.* -0.001 ($P>0.05$) in S15G. One study showed that a deletion of Kiss1r in the neurons of the GnRH axis interrupts the signal of kisspeptin, the protein that induces the secretion of GnRH (gonadotropin-releasing hormone); this results in infertility due to hypogonadism, probably, consanguinity had a negative effect on this mechanism through the interruption of this signal[19] in S15G mice; in the present work, the effects on males were not measured. Something very similar was found in pigs under selection for prolificacy, when this was done with family indices, since an increase in inbreeding depression of three times more than expected without selection and a decrease in the response to selection were seen[20].

RL was affected by consanguinity both in S15G, with a decrease of 4.741 d, and in NS15G, it decreased almost three more days (7.718 d) ($P<0.01$ in both) (Table 3), in a study where there was selection for longer life in mice, it was found that the increase was

related to mutations, which increased the levels of growth hormone in the GH/IGF-1 axis[21], which could be related to a decrease in the life time of the mice, as happened in the lines selected for an index involving litter size and birth weight, without consanguinity[18] in the present work, it decreased in both lines since the selection objective was different.

Postpartum mortality is higher in NS15G, from the first five generations of narrow inbred crossing, compared to S15G, a result similar to that obtained by Sallah[5], both in the selected line and the non-selected line, with mating between half-siblings, where the highest mortality occurred in the intermediate generations. Charlesworth[22] explains this under two hypotheses: 1) dominance, where inbreeding increases the frequency of individuals that express the effects of deleterious mutations or 2) overdominance, where the homozygous would have a lower aptitude due to lack of alleles, with heterozygous advantage that they would maintain by balancing selection at intermediate frequencies in the heterozygous.

As a result of the above, the number of offspring at weaning per parturition in NS15G falls significantly in generations 6 to 10 (1.51 offspring), with a recovery in the following accumulated generations, while in the number of offspring at birth per parturition, it remains in all generations ($P<0.05$) (Table 1) (Figure 3). A recent study[23] revealed that, in litters with less than four offspring at birth, in non-selected mice, there is a higher mortality at weaning, and in the present study, the NS15G line showed less than four offspring at birth on average in the first five generations.

The result in these characteristics was presumable, since, on the one hand, a high inbreeding depression can be expected when performing a narrow inbred cross (brother, sister) and, on the other hand, due to the low heritability (0.024 to 0.063) of the productive index[12], only limited reproduction progress can be expected; a similar result was obtained in litter size with a consanguinity of 0.61 in eight generations of selection with consanguinity in crosses between half-siblings[5].

These results lead to reflect on whether in a selection program in domestic animals, even avoiding crosses between siblings, in generations later, it could occur between relatives, and this induces inbreeding, with the counterproductive effects that were seen here.

In a Holstein cattle improvement program, it was found that with a 1 % increase in consanguinity, milk production in 305 d decreased by 36.3 kg on average, in cows aged 4 to 5 yr, and 2.42 kg of fat[24]. Recently, the implementation of genomic selection was evaluated in the loss of genetic diversity in Holstein and Jersey cattle in North America, due to consanguinity; their results showed an increase in inbreeding from 1.19 to 2.06 % per generation, over a period of 10 yr in Holstein cattle, and warned about the need to implement measures to avoid inbreeding in this type of programs[25]. In the Holstein population of Mexico, it was found that, with levels less than 5 % of consanguinity, no effect was detected in fat or milk protein, however, when inbreeding increased to more

than 5 %, a decrease in milk production of 260 kg per lactation was found, in addition to a loss in fat production of 11 kg and 10 kg in protein with respect to the average of groups with less than 5 %[26].

Conclusions and implications

As the results of NS15G show for a productive index (number of offspring per female per week), inbreeding depression affected its different components, especially in the reproductive characteristics, which could be regulated to a large extent by their simultaneous selection, probably due to a maintenance of genes that favored gonadal development in females and males. The work is relevant because the selection of a productive index in mice in its different components had not been analyzed, in an integral way, in addition to showing that, in a selection program with simultaneous consanguinity, the fixation of desirable alleles in the maintenance of reproductive cycles and the survival of the offspring is favored.

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