

1996

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Nielsen, Merlyn K.; Kochera Kirby, Y. L.; and Clutter, A. C., "Estimates of Heritabilities and Genetic and Environmental Correlations for Left- and Right-Side Uterine Capacity and Ovulation Rate in Mice" (1996). *Faculty Papers and Publications in Animal Science*. 489. <http://digitalcommons.unl.edu/animalscifacpub/489>

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Estimates of Heritabilities and Genetic and Environmental Correlations for Left- and Right-Side Uterine Capacity and Ovulation Rate in Mice^{1,2,3}

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ABSTRACT: Heritabilities for and genetic and environmental correlations between uterine capacity, ovulation rate, and body mass (BM) were estimated in mice. Uterine capacity was defined as the number of fetuses (LUC or RUC for left or right side) in one uterine horn for unilaterally ovariectomized females. Ovulation rate (corpora lutea, LCL or RCL for left or right ovary) was measured on the remaining single ovary in these same females. Data on 1,931 mice from four selection populations were used. Left ovulation rate and LUC were measured on 958 animals, and RCL and RUC of another 972 animals were recorded. Genetic and environmental variances and covariances were estimated simultaneously using an animal model

with a multiple-trait, derivative-free, restricted maximum-likelihood procedure. Averages for heritability and correlation estimates derived from separate analyses of the selection populations are presented below. Heritability of LUC was higher ($.33 \pm .06$) than that of RUC ($.19 \pm .02$). Heritability of LCL and RCL ranged from $.17 \pm .03$ to $.27 \pm .06$, and heritability for BM was $.65 \pm .05$. The genetic correlation between LUC or RUC and LCL or RCL ranged between $.43 \pm .29$ and $.68 \pm .05$, and between LUC and RUC was $.92 \pm .05$. Body mass had a higher genetic correlation with LCL and RCL ($.70 \pm .12$ and $.93 \pm .02$) than with LUC and RUC ($.37 \pm .05$ and $.47 \pm .12$). Environmental correlations between LCL and LUC and RCL and RUC were $.32 \pm .09$ and $.36 \pm .05$, respectively.

Key Words: Mice, Uterine Capacity, Ovulation Rate, Heritability, Genetic Correlation

J. Anim. Sci. 1996. 74:529-534

Introduction

Attempts to explain litter size in terms of components such as ovulation rate and the proportion of ova that become fully formed fetuses or ovulation rate and uterine capacity have enhanced understanding its genetic control. Bennett and Leymaster (1989) pur-

sued elaboration of the ovulation rate, potentially viable embryos, uterine capacity model in swine, showing that such a mathematical model could explain differences in litter size and embryonic survival. Bennett and Leymaster (1990a,b) went on to examine underlying genetic models and expected responses to selection, given assumptions for possible genetic parameters in their model.

Selection for uterine capacity has been practiced in mice at the University of Nebraska and responses in litter size have been reported (Gion et al., 1990; Kirby and Nielsen, 1993). Responses in left and right uterine capacity following selection for various criteria to increase litter size in the same Nebraska study have also been reported (Clutter et al., 1994). Estimates of genetic variances and heritabilities for uterine capacity and genetic covariances (correlations) between uterine capacity and ovulation rate are lacking. The purpose of the present study was to estimate these variances and covariances and then derive estimates of heritabilities and genetic and environmental correlations.

¹Published as paper no. 10823, Journal Ser., Nebraska Agric. Res. Div., Univ. of Nebraska, Lincoln 68583-0908.

²Approved for publication by the Director, Oklahoma Agric. Exp. Sta., Oklahoma State Univ., Stillwater.

³The assistance of J. D. Hauptman, L. D. Van Vleck, S. D. Kachman, L. A. Kriese, K. L. Barkhouse, E.L.A. Ribeiro, B. A. Freking, G. L. Bennett, and K. A. Leymaster is gratefully appreciated.

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Received April 7, 1995.

Accepted December 12, 1995.

Materials and Methods

Experimental Animals. The data were the same as those used in the work by Clutter et al. (1994). The mice were from a long-term selection project for which the selection criteria, selection applied, and selection responses in litter size through 21 generations were described most recently by Kirby and Nielsen (1993). The four criteria for selection were as follows: 1) **LS** = selection on number born to unaltered females; 2) **IX** = selection on an index of $I = 9.21 \times \text{ovulation rate} + 21 \times \text{ova success}$ (success defined as the proportion of ova resulting in fully formed pups at parturition); 3) **UT** = selection on number born to females unilaterally ovariectomized (right ovary excised) at 4 wk of age; and 4) **LC** = randomly selected control. All four selection criteria were applied in each of three replicates for a total of 12 lines.

Selection ceased after 21 generations, and mice sampled to constitute the data for the present study came from Generations 22 and 23, the two generations immediately after selection. All generations of selection took place in the laboratory at the University of Nebraska (UNL). Within each line (criterion-replicate) and generation of the present study, daughters from approximately 30 litters were randomly assigned to either stay in the UNL laboratory or be transported shortly after weaning to the laboratory at Oklahoma State University (OSU). From 40 to 45 females of each line in each generation went to OSU and 40 to 50 females of each line in each generation stayed at UNL. Care was taken to cross-classify laboratory with litter of female. At each laboratory, unilateral ovariectomies (half the females on their left side and half on their right) were performed on the females at approximately 4 wk of age. Wherever possible, full-sib sisters within a laboratory were assigned to each of the two ovariectomy treatments.

After ovariectomy, the females were grown to approximately 9 wk of age and then assigned to mating cages of three to four females per male. Body mass (**BM**) was recorded on the females at this time. Males were from the same line as their mates, and matings were assigned to minimize inbreeding. Evidence of mating plugs was recorded each morning, and pregnant females were euthanatized at 17 d of gestation (mating date = d 0) for collection of the reproductive data. In the event of missing a mating plug, resulting pregnant females were externally palpated to estimate stage of pregnancy and then euthanatized for data collection at approximately the same stage as d 17.

Ovulation rate was determined by counting number of corpora lutea (**LCL** or **RCL** for left or right corpora lutea) on the remaining ovary, and uterine capacity was measured as the number of fully formed fetuses in the functioning uterine horn (**LUC** or **RUC** for left or right uterine capacity). Resulting numbers of females

per laboratory-line-generation-ovariectomy treatment ranged from 16 to 25 (see table 1 of Clutter et al., 1994), and total number of females measured was 1931. Table 1 contains a listing of the numbers of mice measured for each selection criterion group and overall.

Data Analysis. Estimates of the variances and covariances for genetic and environmental effects were derived using the multiple-trait, derivative-free, restricted maximum-likelihood (MTDFREML) program of Boldman et al. (1993) with an animal model that accounted for genetic relationships back to foundation mice. All five variables were run together in the multiple-trait analysis that accepts missing data (mice either had LCL and LUC or RCL and RUC due to the ovariectomy). The data were analyzed by each selection criterion group (LS, IX, UT, and LC) and as a total data set.

The model for each of the selection criterion groups was variable = generation + laboratory + replicate + animal breeding value + random environment. The model for the total data set was variable = generation + laboratory + line (selection criterion-replicate) + animal breeding value + random environment. Only the animal breeding value and random environmental effects were considered random; the other effects were fixed. For a computing strategy, all five variables with all variances and covariances were estimated simultaneously. After convergence to 10^{-6} for the variance of the simplex function, the analyses were restarted. The cycle of repeated starts was stopped when the changes in the *F*-value for the model were less than .01, and the estimation was deemed completed.

Because mice could only have BM, LUC, and LCL or BM, RUC, and RCL, there was no way to estimate the environmental correlation between any combination of the left (LUC and LCL) and right (RUC and RCL) characteristics, and these were forced to zero. The genetic correlations could be estimated through the genetic relationships for all characteristics.

The variability across the four subgroups of data between heritability or correlation estimates was used to derive empirical standard errors. These standard errors thus have three degrees of freedom. The estimates for the data subgroups were averaged, and the same standard error was used for the average and for the estimates from the total data set. The standard errors for estimates calculated from the total data were thus conservative.

An additional set of estimates was derived from a restricted set of the total data. Conceptually, number of fetuses produced by unilaterally ovariectomized females can only be interpreted as uterine capacity if the phenotypic correlation between number of fetuses and number of ovulations is zero (i.e., measurement of uterine capacity is not limited by number of ova [Christenson et al., 1987]). In the total data, the correlation between number of corpora lutea and

Table 1. Number of observations for the five variables by selection populations across the three replicates

Selection population ^a	Variable ^b				
	BM	LUC	RUC	LCL	RCL
IX	498	239	259	239	259
LS	491	249	244	249	244
UT	471	239	241	238	241
LC	460	231	229	231	228
Total	1,920	958	973	957	972

^aSelection criteria in the following were: IX = index of ovulation rate and ova success, LS = number born, UT = number born to unilaterally ovariectomized female, and LC = unselected control.

^bBM = body mass, LUC and RUC = left- and right-side fetuses for unilaterally ovariectomized females, and LCL and RCL = left- and right-side corpora lutea for unilaterally ovariectomized females.

number of fetuses ranged from .26 in the IX animals to .45 for LS mice measured on the right side. By excluding data for mice with low numbers of corpora lutea, hence where uterine capacity was not independent of ovulation rate, we hoped to obtain a data set in which uterine capacity would be independent of ovulation rate.

Table 2 contains data that give a comparison between the total and restricted data sets. Only IX and LS mice with ≥ 15 , UT mice with ≥ 13 , and LC mice with ≥ 12 corpora lutea were included in the restricted data set. The average correlation between number of corpora lutea and number of fetuses across selection populations and sides was reduced from .35 to .20 by eliminating approximately 30% of the data. From bivariate normal theory, one would predict that deleting the lowest 30% of the observations on one variable would reduce the correlation in the remaining data to .73 of the original: $(.35)(.73) = .26$. With finite numbers of observations and characteristics that approach normality, the reduction in correlation was somewhat higher. The same model was used for the restricted as for the total data set. No standard errors were calculated for the heritability and correlation estimates in the restricted data set; these estimates were only derived for the purpose of interpreting estimates from the total data.

Results and Discussion

Phenotypic variances, derived after accounting for the fixed effects in the models, are presented in Table 3. The variances for LUC and RUC were highest in the data set from LS females. The variances for LUC and RUC were considerably higher than those for LCL and RCL.

Although the variances for LUC and RUC were of greatly differing magnitude across the data sets of the four selection groups, the CV were quite similar. The range of CV across the four data groups for the five

Table 2. Number of observations (n) and phenotypic correlations (r) between number of corpora lutea and number of fetuses by selection population and side of reproductive tract in unilaterally ovariectomized females for the total and restricted data sets

Selection population ^a and side	Total data		Restricted data ^b	
	n	r	n	r
IX				
Left	239	.26	169	.15
Right	259	.26	176	.18
LS				
Left	249	.33	179	.11
Right	244	.45	178	.23
UT				
Left	238	.31	170	.14
Right	241	.41	171	.30
LC				
Left	231	.38	177	.28
Right	228	.43	161	.24

^aSee Table 1 for descriptions.

^bIX and LS populations restricted to ≥ 15 corpora lutea, UT restricted to ≥ 13 corpora lutea, and LC restricted to ≥ 12 corpora lutea.

characteristics were as follows: BM, 8.2 to 9.4%; LUC, 28.4 to 32.0%; RUC, 24.6 to 28.2%; LCL, 13.2 to 15.4%; and RCL, 14.8 to 15.8%. The CV for uterine capacity, as measured in the unilaterally ovariectomized female, was essentially the same as that for number of fetuses (28.6%) at term in unaltered females (hence litter size at birth) reported by Clutter et al. (1990). The CV for LCL and RCL agreed well with that for total number of corpora lutea (15.2%) measured in intact females (Clutter et al., 1990).

Estimates of heritabilities and genetic and environmental correlations using the total data are presented in Tables 4 and 5. Table 4 has the average of estimates that were derived from the analyses of the four groups (different selection background) of data. Table 5 has the estimates calculated from the overall total data set.

Estimates of heritabilities and genetic and environmental correlations in the restricted data set are presented in Table 6. The estimates in Table 6 are quite similar to those in Tables 4 and 5. Heritability estimates for LUC and RUC in the restricted data were within the range of the corresponding estimates from the overall and pooled analyses of the total data. Only the estimates of genetic correlation between LUC and RCL and RUC and RCL from the restricted data were outside the range of the corresponding estimates from the two analyses of the total data; one of these correlation estimates was greater and the other less than what was estimated in the total data. Environmental correlations between number of corpora lutea and number of fetuses, only estimable for the same side of the mouse, were lower in the restricted data,

Table 3. Phenotypic variances^a by selection populations and in the total data set

Selection population ^b	Variable ^b				
	BM, g ²	LUC	RUC	LCL	RCL
IX	6.41	10.73	8.40	4.24	5.43
LS	5.05	11.63	10.52	4.68	5.55
UT	5.81	8.58	7.88	3.24	4.61
LC	5.10	6.51	7.35	3.96	4.02
Total	5.60	8.93	8.27	4.19	4.83

^aAfter accounting for fixed effects in the models. See text for models.

^bSee Table 1 for descriptions.

reflecting the lower phenotypic correlations in the restricted compared to the total data set.

Being able to estimate heritabilities and correlations in a data set in which uterine capacity was independent of ovulation rate was the intent in forming the restricted data set. With our limited data, we chose not to eliminate more than 30% because of the initial size of the data set, and thus we were not able to derive a data set with no correlation between ovulation rate and our measure of uterine capacity. By using the restricted data with a correlation of .20 compared with the total data with a correlation of .35, the estimates of the genetic parameters were about the same. Thus, in the remainder of the discussion, we will concentrate only on the estimates from the total data set (Tables 4 and 5).

Although the variances for LUC and RUC in the LS data and for LUC in the IX data were greater than for the other data sets, we did not attempt to equalize these before running the analysis of the total data set. Comparison of the average heritability and correlation estimates pertaining to LUC and RUC to those from the total data analysis (values in Table 4 vs Table 5) was reasonably similar with the exception of the heritabilities and the genetic correlations between LCL and LUC and between LCL and RUC and the environmental correlation between LCL and LUC.

Estimates of heritability for uterine capacity and ovulation rate were consistently greater on the left side than on the right. This is in contrast to the

comparison of sides for estimates using characteristics of intact animals measured in the base population before selection was initiated at UNL (Clutter et al., 1990). In intact mice in the base generation, estimated heritability was the same (.11) for left and right number of corpora lutea, and in the same intact mice, estimated heritability was greater for the number of right-side fetuses (.18) than for the left-side fetuses (.03). Estimates from the present study were also unexpected given the higher responses, using our three selection criteria, for the right side vs the left side in number of corpora lutea and number of fetuses observed in intact animals (Gion et al., 1990) and in the uterine capacity of unilaterally ovariectomized animals (Clutter et al., 1994). Bolet et al. (1994) have also estimated heritability for litter size in unilaterally ovariectomized rabbits. Their estimate (.20 ± .12) derived by REML with an animal model using data from a selection line, is not different from that estimated in the present study.

Our estimates of heritability for ovulation rate, measured on the remaining ovary of the unilaterally ovariectomized mice, were similar in magnitude to the estimates for total ovulation rate in intact mice using sib covariances (.22; Land and Falconer, 1969) and in a combined data set of intact and unilaterally ovariectomized females (.18; Long et al., 1991) but less than that reported for intact females in our base generation (.33; Clutter et al., 1990). Realized heritabilities following selection for total ovulation rate in

Table 4. Estimates (± SE) of heritabilities, genetic correlations, and environmental correlations: averages of the estimates from the four data sets^a

Variable ^b	Variable				
	BM	LUC	RUC	LCL	RCL
BM	.65 ± .05	.37 ± .05	.47 ± .12	.70 ± .12	.93 ± .02
LUC	-.03 ± .05	.33 ± .06	.92 ± .05	.43 ± .29	.54 ± .11
RUC	.19 ± .09	0 ^c	.19 ± .02	.52 ± .31	.68 ± .05
LCL	.05 ± .04	.32 ± .09	0 ^c	.27 ± .06	.73 ± .17
RCL	.17 ± .04	0 ^c	.36 ± .05	0 ^c	.17 ± .03

^aHeritabilities on diagonal, genetic correlations in upper right, and environmental correlations in lower left.

^bSee Table 1 for descriptions.

^cEnvironmental correlations forced to zero because animals could only have left- or right-side measurements.

Table 5. Estimates (\pm SE) of heritabilities, genetic correlations, and environmental correlations: analysis of the total data set^a

Variable ^b	Variable				
	BM	LUC	RUC	LCL	RCL
BM	.64 \pm .05	.44 \pm .05	.51 \pm .12	.87 \pm .12	.98 \pm .02
LUC	-.03 \pm .05	.22 \pm .06	.99 \pm .05	.81 \pm .29	.58 \pm .11
RUC	.22 \pm .09	0 ^c	.13 \pm .02	.84 \pm .31	.65 \pm .05
LCL	-.02 \pm .04	.22 \pm .09	0 ^c	.24 \pm .06	.93 \pm .17
RCL	.22 \pm .04	0 ^c	.36 \pm .05	0 ^c	.10 \pm .03

^aHeritabilities on diagonal, genetic correlations in upper right, and environmental correlations in lower left.

^bSee Table 1 for descriptions.

^cEnvironmental correlations forced to zero because animals could only have left- or right-side measurements.

mice have ranged from .10 (Bradford, 1969) to .31 (Land and Falconer, 1969). In rabbits (Bolet et al., 1994), estimates of heritability of ovulation rate derived from REML analyses in unilaterally ovariectomized females (.30) and intact females (.24) have been similar, accounting for the precision of the estimates. Estimates of heritability of ovulation rate in pigs have been either similar (.17; Neal et al., 1989) or greater (.42; Cunningham et al., 1979) than those in the present study, with the greater being a realized estimate.

The estimated genetic correlation between LUC and RUC was near unity (.92 to .99). Physiological causes of variability in uterine capacity may be much the same for each side, and genes that contribute to size or space (Nielsen et al., 1995), as well as nutrient availability or other contributors to uterine capacity, may largely have universal effects in the animal. Also, in our selection for uterine capacity (UT), all females had right-side ovariectomy, and thus selection pressure was for left-side uterine capacity. Because more response was realized in right than in left uterine performance in intact (Gion et al., 1990) and in unilaterally ovariectomized females (Clutter et al., 1994), one would have expected a high positive genetic correlation between sides.

Table 6. Estimates of heritabilities, genetic correlations, and environmental correlations: analysis of the restricted total data set

Variable ^b	Variable				
	BM	LUC	RUC	LCL	RCL
BM	.63	.37	.27	.83	.94
LUC	.00	.24	1.00	.81	.67
RUC	.23	0 ^c	.19	.75	.59
LCL	.03	.09	0 ^c	.21	.97
RCL	.22	0 ^c	.28	0 ^c	.10

^aHeritabilities on diagonal, genetic correlations in upper right, and environmental correlations in lower left.

^bSee Table 1 for descriptions.

^cEnvironmental correlations forced to zero because animals could only have left- or right-side measurements.

There was no tendency for ovulation rate to be more genetically correlated to uterine capacity on the same side as compared to the opposite side in these unilaterally ovariectomized females. The estimates were near .50 for the averages of the separate data sets and near .75 when derived from the total data set. One would presume that the genetic correlation between ovulation rate and uterine capacity in intact animals is at least .50 and not different across different uterine horns. Our estimate is consistent with that of Long et al. (1991), who previously reported an estimate of the genetic correlation between ovulation rate and uterine capacity in unilaterally ovariectomized mice of .73.

The estimated heritability of body mass, here measured at 9 wk, was approximately .65. This is much higher than the range of estimated realized heritabilities for weight at ages of 6 to 10 wk of .13 to .55 (McCarthy, 1982). Estimated genetic correlations between body mass and ovulation rate (.70 to .98) were higher than between body mass and uterine capacity (.37 to .51). Land (1970) surmised, based on estimates made in selection lines, that the genetic correlation between body mass and ovulation rate in intact mice is positive and greater than .40. A fairly strong realized genetic correlation (.62) between litter size and body mass has been reported by Joakimsen and Baker (1977); Fuente et al. (1986) estimated lower positive realized correlations.

Environmental correlations between uterine capacity and ovulation rate, again as measured in these surgically altered females, were positive and modest in magnitude (.22 to .36). This is in conflict with the suggestion by Long et al. (1991) that the environmental correlation between ovulation rate and number of fetuses (uterine capacity in the unilateral ovariectomy model) must be negative. Environmental correlations with body mass only reached an important magnitude for right-side reproductive performance, in which case they were positive.

Individual estimates for heritabilities and correlations from the selection subgroups of data are not presented for the sake of brevity. Where SE were less than .05, the range in estimates was \leq .18. There were

extremely large SE for the genetic correlations between LCL and LUC and LCL and RUC. These were due to one data set (LS) in which estimates of these correlations were $-.33$ and $-.38$ compared with the other three data sets in which these correlations ranged from $.27$ to $.93$.

For their simulation of selection for litter size in swine, Bennett and Leymaster (1989, 1990b) assumed the heritability of ovulation rate ($.25$) was slightly larger than that for uterine capacity ($.20$); they also assumed no genetic correlation between ovulation rate and uterine capacity. Although heritability estimates in the present study are not significantly different for ovulation rate vs uterine capacity, the genetic correlation between uterine capacity and ovulation rate was significant and probably at least $.50$. Whether mice and pigs are that different, whether the unilaterally ovariectomized and intact animals are quite different, or whether Bennett and Leymaster (1989, 1990a,b) erred in their assumption for the genetic correlation is not yet clear. Modeling litter size in intact mice using an ovulation rate, potentially viable embryos, uterine capacity model may provide part of the answer.

Implications

Genetic variation and covariation exist for ovulation rate and uterine capacity in mice. Simulation of litter size in mice, using parameters to describe genetic and environmental (co)variation of the components, will help in verifying suitability of methods for practicing selection for litter size in livestock species.

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