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Relationships Between Components of Litter Size in Unilaterally Ovariectomized and Intact Rabbit Does[1]

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ABSTRACT: A study was performed to evaluate the use of unilateral ovariectomy for the measurement of uterine capacity in rabbits through a comparison of the relationships between ovulation rate, number of implanted embryos, and litter size in unilaterally ovariectomized (ULO) and intact does. Data from 211 ULO and 323 intact does were analyzed. The animals were derived from a synthetic line previously selected on litter size. Laparoscopy was performed on all does during their second gestation 12 d after mating and the number of corpora lutea and implantation sites were recorded. Intact and ULO does had the same ovulation rate, confirming the presence of compensatory ovarian hypertrophy in the remaining ovary of the ULO does. The number of implantation sites in the ULO group (11.3) approached the number found in the control group (12.6). Embryonic survival (until implantation) was lower ($P < .01$) in ULO does (.77) than in intact does (.88), but fetal survival (after implantation) was the same in both groups. The ULO females produced litters 77% of the size of those of the normal control females. Pre- and postimplantation survivals were not related in intact does but seemed to be related in ULO does through an effect on the number of implantation sites. The coefficient of the regression of number of implantation sites on ovulation rate was positive in control does (.62 ± .06) and was also positive in ULO does (.31 ± .07), showing that a higher ovulation rate would have resulted in a higher number of embryos being implanted in both groups. Litter size had a positive coefficient of regression on number of implanted embryos in both control does (.67 ± .04) and in ULO does (.49 ± .05), showing that a higher number of implantation sites would have produced a higher litter size in both groups. Overall, however, the regression of litter size on ovulation rate was positive in control does (.30 ± .06), but not significantly different from zero in ULO does (.07 ± .08), indicating that unilateral ovariectomy had the desired effect of making litter size independent of ovulation rate.

Introduction

Selection based on litter size has had little success in rabbits (Rochambeau, 1988) and in pigs (Haley et al., 1988). Johnson et al. (1984) have argued that it would be more efficient to select on litter size through its components, ovulation rate and prenatal survival. When ovulation rate alone has been increased by selection in pigs and mice no improvement in litter size has been found, although selection on litter size after selection on ovulation rate (Lamberson et al., 1991) and selection on the two components combined is more promising (see review by Blasco et al., 1993a).

Christenson et al. (1987) suggested use of unilateral hysterectomy and ovariectomy in pigs to eliminate ovulation rate as a component of litter size, therefore allowing uterine capacity to be measured. Uterine capacity was defined as the maximum number of fetuses that the dam is able to support at birth when ovulation rate is not a limiting factor. Bennett and Leymaster (1989) have argued that the consideration of litter size as the result of ovulation rate, potential embryonic viability, and uterine capacity, rather than the product of ovulation rate and prenatal survival, may be more realistic and lead to the development of more effective selection strategies. The factors contributing to variation in uterine capacity are, however, uncertain.

In rabbits, unlike in pigs, it is possible to observe the number of implantation sites by laparoscopy, without damaging litter size (Santacreu et al., 1990). Because transuterine migration is not found in rabbits (Johnson, 1970), unilateral ovariectomy and consequent ovarian hypertrophy result in the uterine horn corresponding to the functional ovary being challenged by double the mean normal number of embryos. The objective of this paper is to examine ovulation rate, number of implanted embryos, litter size and their relationships in unilaterally ovariectomized (**ULO**) does and intact does, to provide insight into the components of uterine capacity and to help define criteria that would enhance selection of rabbits for improved litter size.

Materials and Methods

Animals

Data were collected from a total of 211 unilaterally ovariectomized does (ULO) and 352 intact does. Because it was not possible to record all traits on all animals, the number of animals included in the analyses varied from 195 to 352 according to the trait and treatment group. Data come from 61 ULO does that were contemporary with 59 intact does. Other data on 293 intact does that came from two generations of an elliptical selection experiment on ovulation rate and prenatal survival (Blasco et al., 1993b) were added to the experiment. The remainder of the ULO data came from two generations of animals descended from them and divergently selected on litter size. There were thus five contemporary groups, a group of contemporary ULO and intact does, two groups for the elliptical selection study, and two groups from the ULO selection study. All the animals were derived from a synthetic line selected on litter size, which was founded by mating crossbred males and females of different genetic origin.

Surgical Techniques

For ULO does, left-side ovariectomies were performed before puberty (at 14 to 16 wk of age) via midventral incision. The does were anesthetized using a ketamine-promethazine mixture intramuscularly injected at a rate of 1.2 mL/kg body weight; 5 min later this injection was followed by an intravenous dose of 1.5 mL of the same solution in the marginal ear vein. After grasping the ovary with hemostatic tongs, a ligation was placed around the oviduct and blood vessels and the ovary was removed.

The laparoscopic technique is described in detail by García (1992). This technique allows the number of corpora lutea and the number of sites of implanted embryos to be counted very accurately without affecting litter size (Santacreu et al., 1990).

Traits

Laparoscopy was performed on all does during their second gestation, 12 d after mating, and the numbers of corpora lutea and implanted embryos were recorded. The following traits were analyzed: **OR**, ovulation rate, estimated as the number of corpora lutea; **IE**, number of implantation sites; **LS**, litter size at second parity (total of young rabbits born); **PS**, prenatal survival (LS/OR); **ES**, embryonic survival (IE/OR); and **FS**, fetal survival (LS/IE).

Statistical Analysis

A least squares analysis using the GLM procedures of SAS (1985) was carried out on the following model: $y_{ijkl} = \mu + T_i + G_j + S_{k(j)} + e_{ijkl}$, where μ is the general mean, T_i the treatment effect (intact or ULO females), G_j the contemporary group effect, and $S_{k(j)}$ the selection effect nested within contemporary group effect (to include high and low selection groups in the same generation of ULO females). To examine the relationships between two traits, a covariate was added to the former model: $y_{ijkl} = \mu + T_i + G_j + S_{k(j)} + b\, x_{ijkl} + (b*T)_i\, x_{ijkl} + e_{ijkl}$, where x_{ijkl} is the covariate, b the overall coefficient of regression, and $(b*T)_i$ the interaction between the coefficient of regression and treatment; $b + (b*T)_i$ is the coefficient of regression within the treatment i. If the interaction $(b*T)$ is significantly different from zero, the coefficients of regression of the ULO and intact females are different.

Quadratic relationships between traits were examined by analyzing together data of intact and ULO females (Christenson et al., 1987). Data from only the right side of intact females and ULO females were used to regress number of implanted embryos on ovulation rate. Data from ULO females were multiplied by 2 to scale it to an intact uterine basis prior to regressing litter size on either the number of implanted embryos or on ovulation rate.

To examine the accuracy of the regressions, the coefficient of determination R^2 and the R^2/R^2_{max} were calculated. R^2_{max} is the maximum R^2 attainable by fitting one effect for each class of the covariate (e.g., one effect for each group of animals with the same ovulation rate) rather than fitting it as a linear covariate. R^2_{max} is less than unity because there are repeat observations within each class of the covariate that have different values of the independent variate (e.g., animals with the same ovulation rate may have different litter sizes). Thus R^2/R^2_{max} represents the proportion of the explainable variation for which the model accounts (Draper and Smith, 1981).

Results and Discussion

Intact and ULO does had similar ovulation rates ($P > .05$) (Table 1), confirming compensatory ovarian

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Table 1. Least squares means and standard deviations of the ovulation rate (OR), number of implantation sites (IE), preimplantation survival (ES), postimplantation survival (FS), prenatal survival (PS), and litter size at birth in the second gestation (LS) in unilaterally ovariectomized does (ULO) and intact does

	Intact does				ULO does				
Trait	n	Mean	SD	CV	n	Mean	SD	CV	Sig.[a]
OR	323	14.4	2.25	.16	211	14.9	2.28	.15	NS[b]
IE	323	12.6	2.51	.20	210	11.3	2.79	.25	*
ES	323	.88	.14	.16	210	.77	.19	.25	**
FS	323	.77	.16	.21	195	.73	.18	.25	NS
PS	323	.68	.18	.27	196	.55	.19	.35	**
LS	352	10.1	2.72	.27	196	7.8	2.34	.30	**

[a]Sig.: test of difference between treatments.
[b]NS: not significant.
*$P \leq .05$.
**$P \leq .01$.

hypertrophy in the remaining ovary of the ULO does, as reported by Fleming et al. (1984) in rabbits, Clutter et al. (1990) in mice, and Christenson et al. (1987) in pigs. A hypothesis of the model of uterine capacity proposed by Christenson et al. (1987) in pigs is that by doubling ovulation rate of an ovary it is possible to make litter size independent of ovulation rate in the corresponding uterine horn. To obtain this independence, the variation of ovulation rate should not be much higher in the ovary that has doubled its ovulation rate (otherwise some does will still have ovulation rate as a limiting factor). In our data, the standard deviations of ovulation rate are indeed very similar in the control and ULO females (Table 1).

Only two cases of transuterine migration were found and removed from the data base. In both cases only one embryo migrated. The number of implantation sites in the ULO does (11.3), although less ($P < .05$) than the number found in the intact does (12.6), was not markedly reduced. However, embryonic survival was lower in these does ($P < .01$). The number of implantation sites is determined by both the uterus

and the number of embryos that have survived. The number of embryos that are capable of being implanted depends on the fertilization rate, the quality of the ova (Torres, 1982), and the length of the ovulation process, which can lead to competition among embryos at different stages of development (Pope and First, 1985; Bazer et al., 1990, in pigs). Bolet and Theau-Clément (1994) have found differences in fertilization rate associated with genetic origin of rabbits. Lamberson et al. (1989), in mice, reported a higher pre-implantation mortality in ULO females and suggested that the main causes could be immature ova and abnormal embryos. Koening et al. (1986) found a higher percentage of immature ova in a line of pigs selected for high ovulation rate. Besides, the number of implantation sites can be determined by the uterus, as noted above. Adams (1962) and Hafez (1964) transferred a large number of embryos in rabbit does, obtaining large differences between does in number of implantation sites. These differences could be due to failures in the transfer technique as well as to differences between does in implantation

Table 2. Regression coefficients (b) with standard errors of implantation sites (IE), litter size at birth (LS), preimplantation survival (ES), and prenatal survival (PS) on ovulation rate (OR), postimplantation survival (FS), and LS on IE, and FS on ES in unilaterally ovariectomized does (ULO) and intact does[a]

		Intact does				ULO does				
Y	X	n	b ± SE	R^2	R^2/R^2_{max}	n	b ± SE	R^2	R^2/R^2_{max}	Sig.[b]
IE	OR	323	.62 ± .06	.32	.78	210	.31 ± .07	.14	.52	**
LS	OR	323	.30 ± .06	.08	.53	196	.07 ± .08	.09	.43	*
ES	OR	323	−.014 ± .004	.05	.44	210	−.031 ± .005	.18	.72	*
PS	OR	323	−.023 ± .004	.09	.68	196	−.031 ± .005	.21	.67	NS[c]
FS	IE	323	−.010 ± .004	.04	.56	195	−.023 ± .004	.13	.76	**
LS	IE	323	.67 ± .04	.40	.80	195	.49 ± .05	.40	.95	**
FS	ES	323	−.01 ± .07	.02	.09	195	−.26 ± .06	.07	.21	**

[a]R^2/R^2_{max} = proportion of explainable variation accounted for (see text for further details). Y = dependent variable; X = covariate.
[b]Sig.: test of difference between regression coefficients for the two treatments.
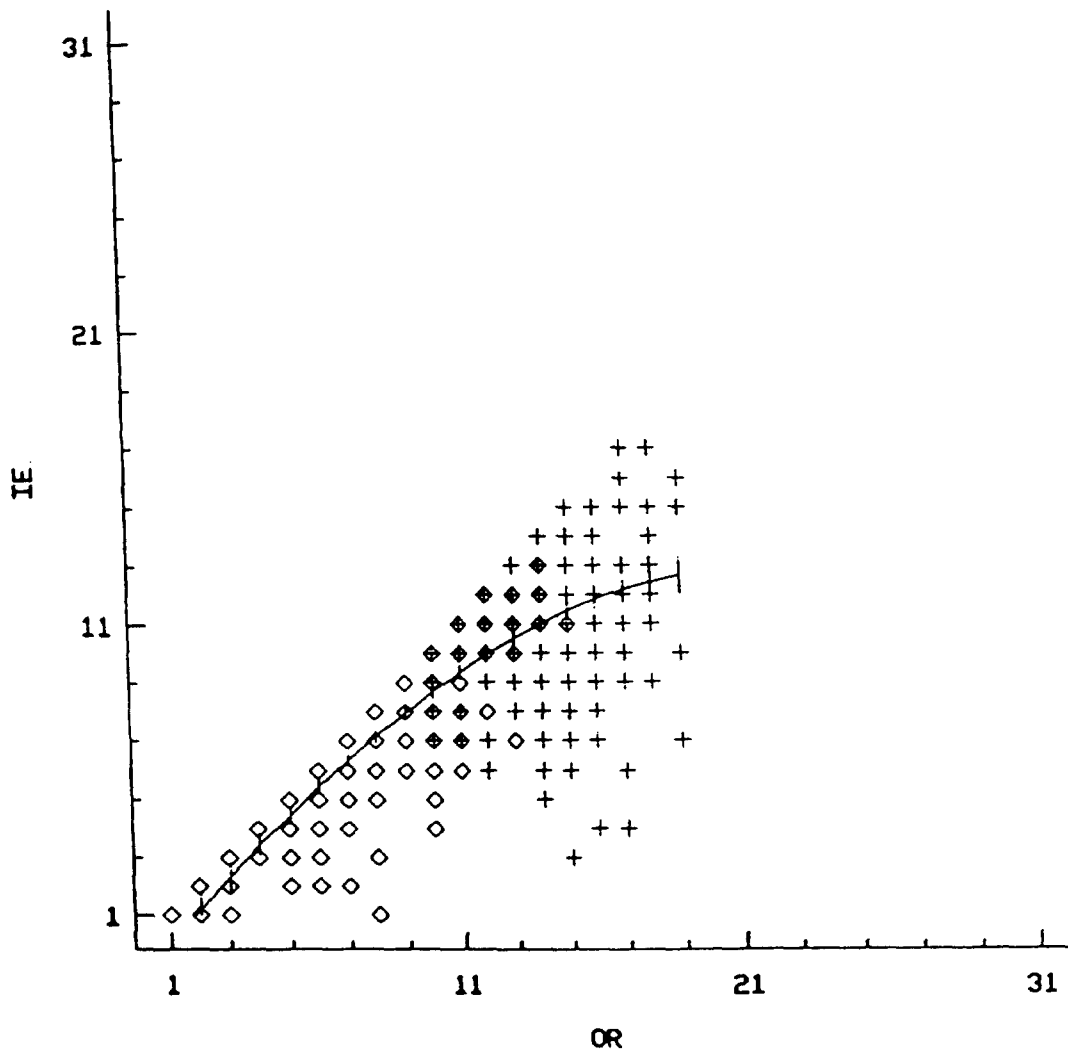[c]NS: not significant.
*$P \leq .05$.
**$P \leq .01$.

Figure 1. Relationship between implantation sites (IE) and ovulation rate (OR) with 95% intervals for means. Each point can represent several does. ◊ = Data of right side of intact does. + = Data of ULO does. IE = (−1.25 ± .50) + (1.28 ± .10)OR + (−.03 ± .00)OR².

capacity. There is some variation among females in the amount and composition of uterine secretions (Adams, 1962, in rabbits; Dziuk, 1968, Ulberg and Rampacek, 1974, Bazer et al., 1990, in pigs), which could have some influence on the number of embryos that will be successful. Adams (1958), in rabbits, found that the peak period of mortality occurred immediately after the transition from morula to blastocyst, when the assistance of special uterine factors may be required.

Fetal survival was not reduced in the ULO group compared with the control group ($P > .05$). This is a rather surprising result, because it has been assumed that fetal mortality would be more important as the gestation progressed after implantation, due to competence between fetuses for the space and nutrients (Adams, 1962; Hafez, 1964).

The ULO does produced litters 77% the size of those of the normal females. This shows the high capacity of

the uterus when it is challenged with a high number of embryos. However, whether litter size in ULO does was in this case a good estimator of the uterine capacity is a more complex question. If a higher preimplantation mortality in ULO does is due to immature ova or early embryonic mortality not related to uterine factors, litter size would not clearly represent their uterine capacity.

Table 2 shows the results of the regression analyses. The relationships between ovulation rate, number of implanted embryos, and litter size in intact does have been previously studied by Santacreu et al. (1992). Litter size is positively associated with ovulation rate in control does but is independent of it in ULO does, as has been found in pigs (Christenson et al., 1987). The coefficient of regression for number of implantation sites on ovulation rate, although reduced compared with that for control does, was positive in ULO does, showing that the ULO does

could have implanted a higher number of embryos if the ovulation rate had been higher. At 86 d of gestation, Christenson et al. (1987) found similar coefficients of regression for pigs (i.e., .60 for intact gilts and .41 for unilaterally hysterectomized-ovariectomized gilts).

The increment of embryonic mortality when ovulation rate increases was shown by the higher negative coefficient of regression of ES on OR in ULO females. Table 2 also shows the regression of litter size on number of implantation sites. Because litter size still has a positive coefficient of regression in ULO does, it seems that a higher number of implanted embryos would have resulted in a higher litter size in these does.

Pre- and postimplantation survivals (ES and FS, respectively) were not associated in intact does but were in ULO does. A high embryonic survival in ULO

does resulted in a high number of implanted embryos, which in turn produced a higher fetal mortality, perhaps because the capacity of the uterus was exceeded. In intact does, however, increased embryonic survival did not result in sufficient implanted embryos to challenge the uterine capacity and produce this mortality. Thus, factors affecting embryonic and fetal survival may differ if differences in implantation rate are accounted for, and several authors have proposed that the causes of prenatal mortality are not the same in different periods of gestation (Adams, 1960, 1962, in rabbits; Bazer et al., 1990, Dziuk, 1992, in pigs).

Figure 1 shows the relationship between ovulation rate and number of implantation sites in the right horn in both intact and ULO does. The relationship is linear within each group (the quadratic coefficient was not different from zero in both cases, $P > .05$), but
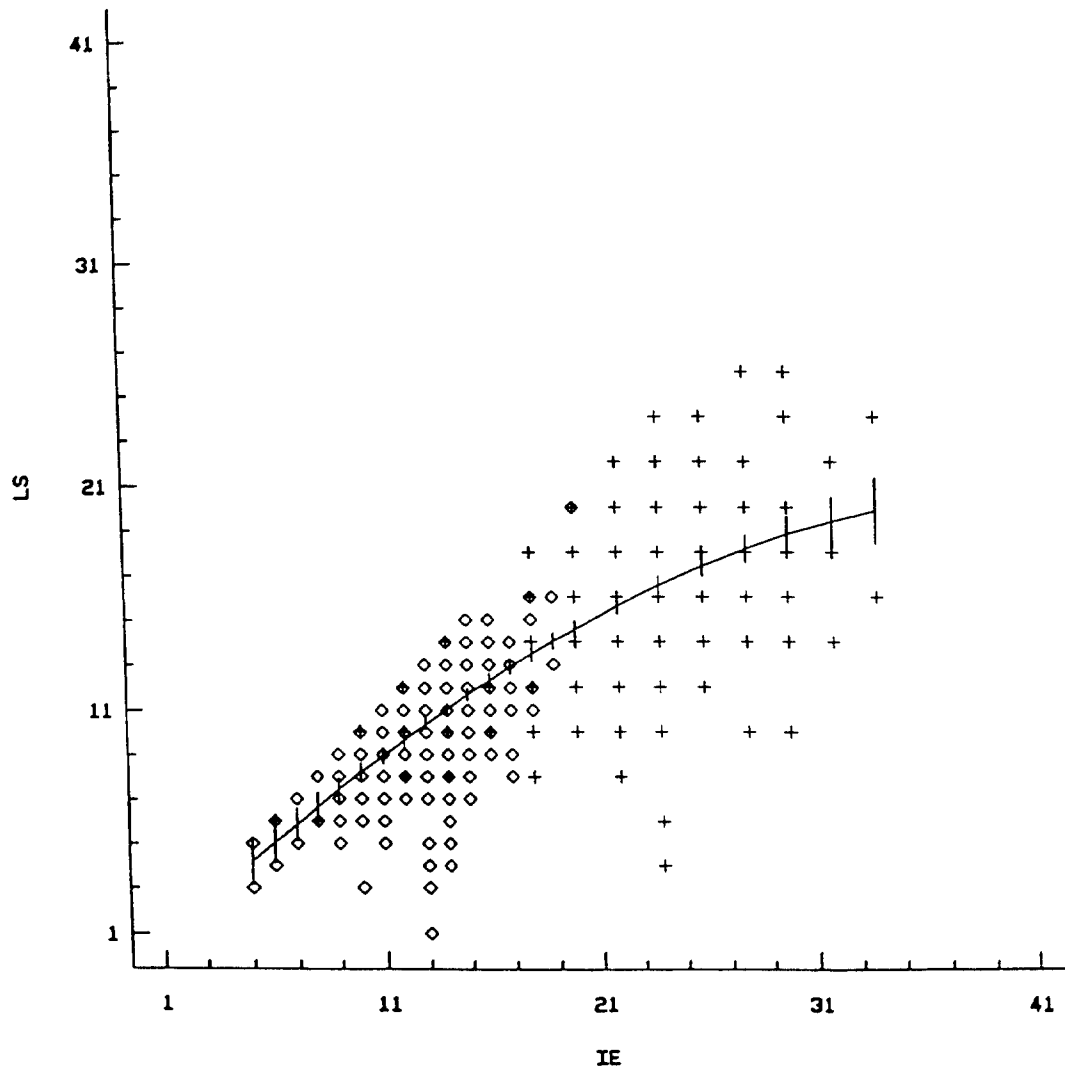

Figure 2. Relationship between litter size (LS) and implantation sites (IE) with 95% intervals for means. Each point can represent several does. ◊ = Data of intact does (both sides). + = Data of ULO does. LS = (.30 ± .95) + (.99 ± .12)IE + (−.01 ± .00)IE^2.
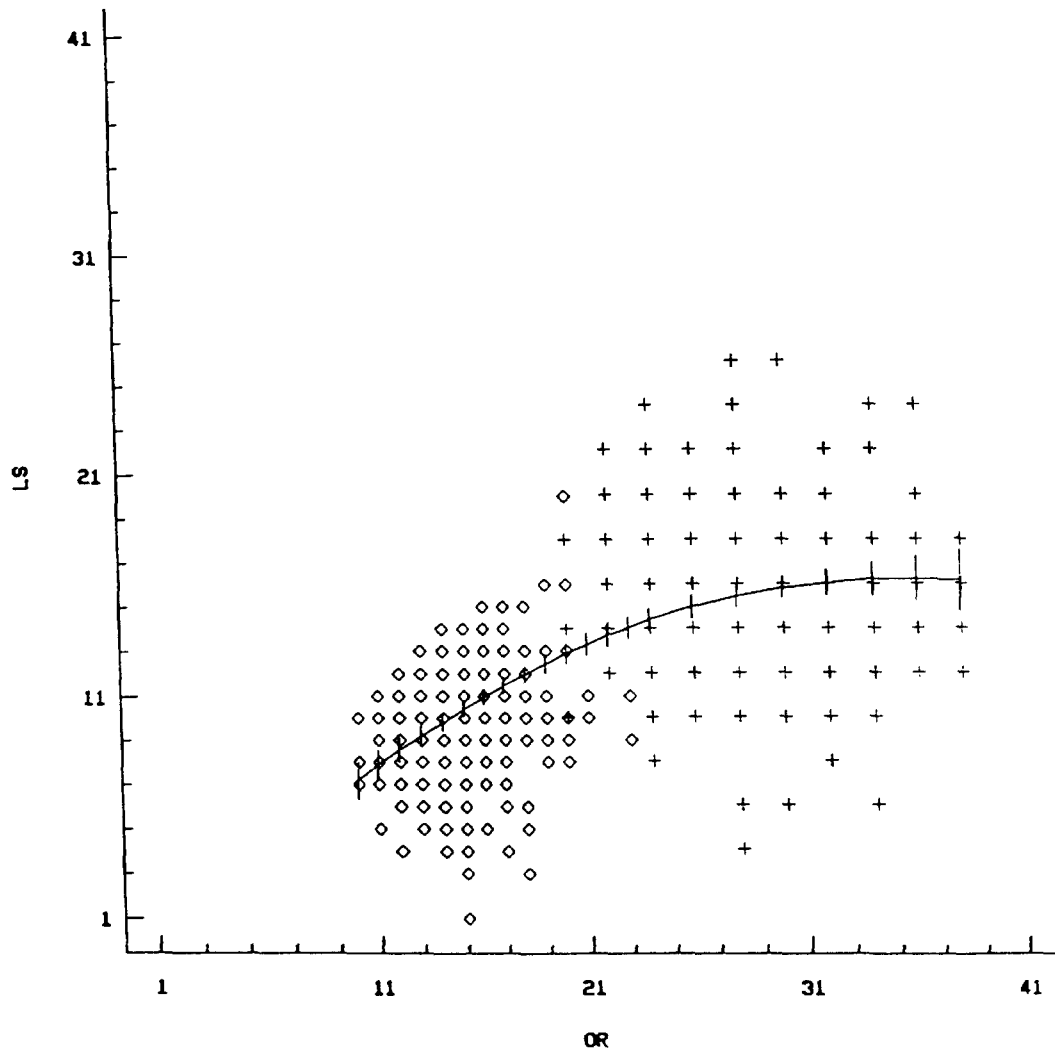
Figure 3. Relationship between litter size (LS) and ovulation rate (OR) with 95% intervals for means. Each point can represent several does. $\lozenge$ = Data of intact does (both sides). + = Data of ULO does. LS = $(-1.46 \pm 1.61) + (.83 \pm .16)$OR $+ (-.01 \pm .00)$OR^2.

when both groups are considered together, this relationship has a significant quadratic coefficient (P < .05). The same happens with the relationships between number of implantation sites and litter size (Figure 2) and with the relationship between ovulation rate and litter size (Figure 3). In Figures 2 and 3 the data from the one side of ULO females have been multiplied by 2 to allow the comparison of ULO and control does on the basis of two uterine horns (Christenson et al., 1987), because, unlike the implantation data, litter size per uterine horn was not available in intact does. No information is available in the literature on ovulation rate, number of implanted embryos, and litter size of the same gestation in ULO females in mice, pigs, or rabbits. Christenson et al. (1987) presented a similar pattern of ovulation rate and litter size in pigs: when all the data are considered together, the relationship is not linear, showing how an increment in ovulation rate produces

an increasing prenatal mortality. In rabbits the relationships between ovulation rate, number of implanted embryos, and litter size were linear in intact females in our population because the numbers of ova released (and implanted embryos) were not high enough to lead to a plateau.

Implications

Selection on litter size in unilaterally ovariectomized does has been proposed as a way to improve uterine capacity in rabbits (including in this concept both the number of embryos that a uterine horn can accept for implantation and the number of fetuses that can be carried through gestation). Selection on uterine capacity could be a more efficient way of improving litter size in rabbits than direct selection on litter size, although more research is needed to confirm this possibility.

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