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EFFECT OF INCREASED OVULATION RATE ON EMBRYO AND FOETAL SURVIVAL AS A MODEL FOR SELECTION BY OVULATION RATE IN RABBITS

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Abstract: Selection for ovulation rate in prolific species has not improved litter size, due to an increase in prenatal mortality, with most mortality observed in the foetal period. The aim of this study was to investigate the magnitude and timing of embryo and early foetal survival in females with high ovulation rate using hormonal treatment as a model for selection by ovulation rate. Two groups of females (treated and untreated) were used. Treated females were injected with 50 IU equine chorionic gonadotropin 48 h before mating. Females were slaughtered at 18 d of gestation. Ovulation rate (OR), number of implanted embryos (IE), number of live foetuses at 12 and 18 d (LF_{12} and LF_{18}, respectively) were recorded. In addition, embryo survival (ES=IE/OR), foetal survival at 18 d of gestation (FS_{LF18}=LF_{18}/IE), foetal survival between 12 and 18 d of gestation ($FS_{LF18/LF12}$=LF_{18}/LF_{12}) and prenatal survival (PS_{LF18}=LF_{18}/OR) were estimated. For each female, the mean and variability of the weight for live foetuses (LFWm and LFWv, respectively) and their placentas (LFPWm and LFPWv, respectively) were calculated. Treated females had a higher ovulation rate (+3.02 ova) than untreated females, with a probability of 0.99. An increase in the differences (D) between treated and untreated females was observed from implantation to 18 d of gestation (D=–0.33, –0.70 and –1.28 for IE, LF_{12} and LF_{18}, respectively). These differences had a low accuracy and the probability that treated females would have a lower number of foetuses also increased throughout gestation (0.60, 0.70 and 0.86 for IE, LF_{12} and LF_{18}, respectively). According to the previous results for OR and LF_{18}, treated females showed a lower survival rate from ovulation to 18 d of gestation (D=–0.12, *P*=0.98 for PS_{LF18}). Treated females also had lower embryo and foetal survival (D=–0.10 and *P*=0.94 for ES and D=–0.08 and *P*=0.93 for FS_{LF18}). Main differences in foetal survival appeared from 12 to 18 d of gestation (D=–0.09 and *P*=0.98 for $FS_{LF18/LF12}$). Unexpectedly, treated females showed similar foetus weight and higher foetal placenta weight than untreated females (D=0.25 g, *P*=0.98) and lower variability for these traits (D=–0.02 g, *P*=0.72 for LFWv and D=–0.05 g, *P*=0.83 for LFPWv). These results are not related to a lower number of IE or LF_{18}. Thus, the effect of increasing by three ova in rabbits leads to a lower embryo and early foetal survival. There seems to be no relationship between foetal mortality and foetus weight.

Key Words: early foetal survival, embryo survival, high ovulation rate, rabbit.

INTRODUCTION

Increased ovulation rate has been considered as a way to improve litter size in both rabbits and pigs. However, selection for ovulation rate did not improve litter size, due to an increase in prenatal mortality (Laborda *et al.,* 2011, 2012a in rabbits; Leymaster and Christenson, 2000; Rosendo *et al.,* 2007 in pigs). In rabbit selection experiments for ovulation rate, most of the mortality was observed during the foetal period, which comprises the period from implantation to birth (Laborda *et al.,* 2012a). Similar results were found in a line selected for ovulation rate in pigs (Freking *et al.,* 2007). A better knowledge of the timing of foetal mortality in females with high ovulation rate is

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needed to propose alternative ways of improving litter size. In rabbit, most foetal mortalities occur until the 18th d of gestation. Early foetal period (between the 8th and 18th d of gestation) is critical for foetal survival, as the placenta initiates controlling foetal nutrition during this period (Adams, 1960a). Moreover, placental development is related to foetal growth and survival (Argente *et al.,* 2003 in rabbits; Knight *et al.,* 1977 in pigs).

When there is no control population to study the effect of selection for ovulation rate on survivals traits, the effect of selection for ovulation rate can be modelled by implementing a low dose hormonal treatment in females, as previously proposed by van der Waaij *et al.* (2010) in pigs. The aim of this study was to investigate the magnitude and timing of embryo and early foetal survival in females with high ovulation rate, using hormonal treatment as a model for selection by ovulation rate. Furthermore, the foetus and placenta weights were studied to assess the influence of a high ovulation rate on foetal and placental development at 18 d of gestation.

MATERIALS AND METHODS

All experimental procedures involving animals were approved by the Universitat Politècnica de València Research Ethics Committee.

Animals

A total of 51 multiparous rabbit females from a line selected by ovulation rate and litter size for 14 generations were used. Details of this line can be found in Ziadi *et al.* (2013). Animals were housed at the selection farm of the Universitat Politècnica de València in individual cages and fed a commercial diet. Animals were reared under a photoperiod of 16-h light: 8-h dark.

Treatment with eCG

Females were randomly distributed in 2 groups: (i) control group with 27 females, and (ii) hormonal treated group in which 24 does were treated i.m. with a dose of 50 IU equine chorionic gonadotropin (eCG; Folligon®, Intervet Ireland Ltd, Dublin) 48 h before mating. This dose was used because previous results had shown an increase in the number of ova without reducing the early embryo survival and development (Mehaisen *et al.,* 2005). Natural mating was carried out 10 d after the last parturition. Abdominal palpation was performed 12 d after mating. Pregnant females were slaughtered by stunning and exsanguination at d 18 of gestation.

Traits

After slaughter, the complete reproductive tract was removed. Ovulation rate (OR) was determined by counting the number of corpora lutea in both ovaries. Both ovaries were weighted (OW). Implantation sites were determined by uterine horn examination and classified according to presence of atrophic maternal placenta, foetal placenta, and dead and/or live foetuses. The following traits were recorded: number of sites with presence of only atrophic maternal placenta (MP), number of sites with presence of maternal and foetal placenta without foetus (FP), number of sites with presence of both placentas and dead foetus (DF_{18}) and number of sites with presence of both placentas and live foetus (LF_{18}). All foetuses and corresponding foetal placentas were removed from the uterine horn. Live foetuses were individually weighed after removal of placental membranes and fluids. Foetal placentas were also weighed, distinguishing between live and dead foetus placenta. For each female, the mean of the weight for live foetuses (LFWm), foetal placenta for live foetuses (LFPWm) and foetal placenta for dead foetuses (DFPWm) were estimated. Additionally, the variability of the live foetus weight (LFWv) and live foetus placental weight (LFPWv) for each female was calculated as a SD.

Number of implanted embryos (IE) was estimated as the sum of MP, FP, DF_{18} and LF_{18}. Total number of foetuses at 18 d of gestation (TF_{18}) was estimated as the sum of LF_{18} and DF_{18}. Foetal placenta initiates the control of foetal nutrition around 12 d of gestation, thus the number of live foetuses at 12 d (LF_{12}) was estimated as the number of implanted embryos minus the number of sites with only maternal placenta (LF_{12}=IE–MP). Embryo survival (ES) was calculated as the ratio between IE and OR. Foetal survival at 12 d of gestation (FS_{LF12}) was estimated as the ratio between LF_{12} and IE.

Similarly, foetal survival at 18 d of gestation (FS_{LF18}) was estimated as LF_{18}/IE. Besides, $FS_{LF18/LF12}$ was estimated as the ratio between LF_{18} and LF_{12}. Prenatal survival (PS_{LF18}) was estimated as the ratio between LF_{18} and OR.

Statistical Analyses

The analysis was based on Bayesian methods. Bounded uniform priors were used for all unknowns, and data were assumed to be normally distributed.

To estimate differences between effects, the following model was fitted for OR, OW, IE, LF_{12}, $LF_{18,}$ TF_{18} and survival rates and weight traits: $y_{ijk} = T_i + L_j + T \times L_{ij} + e_{ijk}$, where T_i is the effect of the treatment (treated and control group), L_j is the effect of the lactation status (lactated and non-lactated female), $T \times L_{ij}$ is the effect of the interaction (treatment and lactation status) and e_{ijk} is the residual effect. Weight traits and their variability were also analysed with the same model including number of foetus at 18 d of gestation as a covariate.

Marginal posterior distributions of all unknowns were estimated by Gibbs Sampling (Sorensen and Gianola, 2002). The TM program developed by Legarra *et al.* (2008) was used for all Gibbs sampling procedures. After some exploratory analyses, we used one chain of 1,000,000 samples, discarding the first 200,000 and saving every 100 thereafter. The Monte Carlo standard error (MCse) was estimated and convergence was tested using the Z criterion of Geweke as shown by Sorensen and Gianola (2002).

RESULTS AND DISCUSSION

Only one selection experiment for ovulation rate has been carried out in rabbits. In that experiment, ovulation rate responded to selection, but no correlated response in litter size was obtained due to a decrease in prenatal survival (Laborda *et al.,* 2012a). There is little information on magnitude and timing of prenatal mortality in rabbits selected for ovulation rate. This selection process can be modelled implementing an adequate hormonal treatment in females. Comparing hormonal treated and untreated females allows us to assess the effect of the increased ovulation rate on prenatal survival and its components: embryo and foetal survival.

Table 1: Raw mean, standard deviation (SD) and coefficient of variation (CV) for studied traits for untreated females.

Trait	Mean	SD	CV (%)
OR	17.35	3.59	20.7
OW	1.50	0.27	18.1
IE	11.67	4.18	35.8
LF_{12}	10.41	4.30	41.3
TF_{18}	9.15	3.93	43.0
LF_{18}	8.93	3.94	44.2
ES	0.66	0.19	28.7
FS_{LF12}	0.87	0.13	15.4
$FS_{LF18/LF12}$	0.85	0.13	15.8
FS_{LF18}	0.75	0.17	22.5
PS_{LF18}	0.50	0.19	37.8
LFWm	1.93	0.37	19.3
LFPWm	2.24	0.42	18.9
DFPWm	0.60	0.31	51.9
LFWv	0.24	0.10	41.8
LFPWv	0.43	0.15	34.4

OR=Ovulation rate, OW=Ovaries weight (g), IE=Number of implanted embryos, LF_{12}=Number of live foetuses at 12 d of gestation, TF_{18}=Total number of live foetuses at 18 d of gestation, LF_{18}=Number of live foetuses at 18 d of gestation, ES= Embryo survival, FS_{LF12}=Foetal survival of live foetuses at 12 d of gestation, FS_{LF18}=Foetal survival of live foetuses at 18 d of gestation, $FS_{LF18/LF12}$=foetal survival between 12 and 18 d of gestation, PS_{LF18}=Prenatal survival of live foetuses at 18 d of gestation, LFWm=Live foetus weight (g), LFPWm=Live foetus placental weight (g), DFPWm=Dead foetus placental weight (g), LFWv=Variability on live foetus weight (g), LFPWv=Variability on live foetus placental weight (g).

Raw means and SD for untreated females are shown in Table 1. Ovulation rate was higher than in other maternal lines selected by litter size (15 ova; García and Baselga, 2002) and uterine capacity (14.8; Santacreu *et al.,* 2005), as the females used in this experiment came from a line selected for ovulation rate and litter size. Similar ovulation rate, around 16.4 ova, was published by Laborda *et al.* (2011) in a line selected by ovulation rate over 10 generations. Number of implanted embryos was within the range of all lines previously quoted, and embryo survival was lower (0.66 *vs.* 0.82 to 0.87). There is only scarce information about foetal traits at 18 d of gestation. Similar numbers of live foetuses at 18 d of gestation (LF_{18}) but lower FS_{LF18} (0.75 *vs.* 0.90) and PS_{LF18} (0.50 *vs.* 0.73) were obtained comparing with a line selected for uterine capacity (Argente *et al.,* 2008). Regarding the weight, similar LFWm and higher LFPWm from untreated females were found compared to the line quoted previously, which had similar IE (Argente *et al.,* 2006).

Ovulation rate, number of implanted embryos and foetuses

Features of the estimated marginal posterior distributions of the differences between treated and untreated females for OR, OW, IE, LF_{12}, TF_{18} and LF_{18} are shown in Table 2. All MCse were very small and lack of convergence was not detected by the Geweke test. Marginal posterior distributions were approximately normal, thus mean, mode and median were similar.

Treated females had roughly 3 ova more than untreated females (*P*=0.99, Table 2), in agreement with previous results in rabbits (Mehaisen *et al.,* 2005). Low concentration of eCG was used to increase ovulation rate to a level similar to that obtained after ten generations of selection for ovulation rate (Laborda *et al.,* 2012b). In this selection experiment, an increase of 2.1 ova [highest posterior density region of the difference at 95% (HPD95%)=1.3, 2.9] was estimated but no correlated response in litter size was found due to a decrease in prenatal survival (–0.12 kits). In the present experiment, the probability that treated females would show 1 or 2 ova more than the untreated females was high, 0.95 and 0.80, respectively. Moreover, the probability of a difference between treated and untreated females higher than 6 ova was close to zero (0.01). Based on results obtained by Mehaisen *et al.* (2005), we assume that the low increment in ovulation rate obtained in the present work using 50 UI eCG did not affect early embryo survival and development. Thus, the increase in ovulation rate using this hormone and dose could be a good model to provide some insight into the negative consequences on prenatal survival due to increased ovulation rate by selection. A disadvantage of using a hormonal treatment model is that the effect of selection for ovulation rate on other genetic correlated traits is not considered. There was no important difference between treated and untreated females for OW (Table 2). No information was found about the effect of increased OR on the ovary weight when superovulation treatment was applied. Comparing intact and unilateral ovariectomised females, Argente *et al.* (2008) reported the increased ovulation rate as a reason for increasing ovary weight; these authors showed that the ovary weight augmented 50% when a duplication of OR in the remaining functional ovary was achieved.

An increase in the posterior mean differences (D) between treated and untreated females was observed from implantation (IE) to 18 d of gestation (LF_{18}); D=–0.33, –0.70 and –1.28 for IE, LF_{12} and LF_{18}, respectively. These

Table 2: Mean of the posterior distribution for treated and untreated females and features of the marginal posterior distributions of the differences between treated and untreated females for ovulation rate (OR), ovaries weight (OW, g), number of implanted embryos (IE), number of live foetuses at 12 d of gestation (LF_{12}), total number of foetus at 18 d of gestation (TF_{18}), and number of live foetuses at 18 d of gestation (LF_{18}).

Trait	Treated	Untreated	D	$HPD_{95\%}$	*P*
OR	20.54	17.45	3.02	0.60 ; 5.35	0.99
OW	1.50	1.50	–0.01	–0.19 ; 0.17	0.53
IE	11.41	11.68	–0.33	–3.03 ; 2.30	0.60
LF_{12}	9.78	10.43	–0.70	–3.33 ; 1.88	0.70
TF_{18}	8.00	9.16	–1.21	–3.69 ; 1.21	0.84
LF_{18}	7.70	8.93	–1.28	–3.67 ; 1.06	0.86

D=Posterior mean of differences between treated and untreated females, $HPD_{95\%}$=Highest posterior density region of the difference at 95%, *P*=Probability of the difference being higher than zero when D>0 or lower than zero when D<0.

estimated differences had a low accuracy (see high $HPD_{95\%,}$ Table 2) and the probability that treated females would have a lower number of foetuses also increased along gestation (P=0.60, 0.70 and 0.86 for IE, LF_{12} and LF_{18}, respectively). Difference between treated and untreated females for TF_{18} was similar to difference for LF_{18}, so similar numbers of dead foetuses were reached.

Survival rates

According to the previous results for OR and LF_{18}, treated females showed a lower survival rate from ovulation to 18 d of gestation (D=–0.12, P=0.98 for PS_{LF18}, Table 3). In the rabbit selection experiment for ovulation rate cited earlier, the estimated difference between selected and control lines for prenatal survival from ovulation to birth was the same, –0.12 ($HPD_{95\%}$=–0.20, –0.04; Laborda *et al.,* 2012b). The results confirmed that a moderate increased of ovulation rate by hormonal treatment could be used to assess the timing of prenatal mortality in ovulation rate selection experiments.

In rabbit, it is accepted that prenatal survival comprises an embryonic period (before implantation, day 7) and a foetal period (after implantation) (Mocé *et al.,* 2010). For embryonic period, treated females showed lower survival (D=–0.10 and P=0.94 for ES; Table 3). Higher embryo loss has been reported in selected females for ovulation rate in rabbits and pigs. To our knowledge, there is no information about the effect of high ovulation rate on fertilisation rate. Usually, embryo mortality includes fertilisation failures and embryo losses. After 10 generations of selection by ovulation rate in rabbits, a negative correlated response in embryo survival, –0.05 ($HPD_{95\%}$=–0.12, 0.02), was observed when the selected line was compared to a control line (Laborda *et al.,* 2012b). Besides, in pigs, Koenig *et al.* (1986) found a higher proportion of immature ova in selected females for high ovulation rate compared to unselected females, and in superovulated females compared to naturally ovulated ones; they suggest that immaturity of ova may account for a substantial proportion of prenatal mortality in gilts with high ovulation rate, either before or after implantation. Moreover, a second cause of this increase in embryo mortality could be a higher variability in embryonic development as a result of longer processing time of ovulation. Oocytes which ovulate first are fertilised earlier and advance the uterine secretions (Torres *et al.,* 1984 in rabbits; Pope, 1988 and Xie *et al.*, 1990 in pigs; Wilmut *et al.,* 1986 and Al-Shorepy *et al.,* 1992 in mice). Asynchrony between embryonic development and uterine secretions can cause embryo mortality, as shown in asynchronous embryo transfer experiments in rabbits (Wintenberger-Torres, 1974; Torres *et al.,* 1987). For foetal period comprised from implantation to 18 d of gestation, treated females also had lower survival (D=–0.08 and P=0.93 for FS_{LF18}; Table 3). A decrease in foetal survival, from implantation to birth, has also been reported in rabbit females with high ovulation rate after 10 generations of selection for ovulation rate, –0.12 ($HPD_{95\%}$=–0.19, –0.6; Laborda *et al.,* 2012b). Based on the presence or absence of foetal placenta by uterine horn examination, foetal survival from implantation to 12 d of gestation was estimated and no difference between treated and untreated females was found (D=–0.01 and P=0.63 for FS_{LF12}; Table 3). Thus, the main difference in foetal survival appeared from 12 to 18 d of gestation (D=–0.09 and P=0.98 for $FS_{LF18/LF12}$). The number of dead foetuses present at 18 d of gestation is very low in both treated and untreated females (see mean values for TF_{18} and LF_{18}, Table 2), therefore differences in foetal survival probably occur shortly after 12 d of gestation. This is a critical period for foetal survival because the placenta begins controlling foetal nutrition (Adams, 1960b).

Table 3: Mean of the posterior distribution for treated and untreated females and features of the marginal posterior distributions of the differences between treated and untreated females in embryo survival (ES), foetal survival of live foetuses at both 12 (FS_{LF12}) and 18 (FS_{LF18}) days of gestation, foetal survival between 12 and 18 d of gestation ($FS_{LF18/LF12}$), prenatal survival of live foetuses at 18 d of gestation (PS_{LF18}).

Trait	Treated	Untreated	D	$HPD_{95\%}$	P
ES	0.56	0.66	–0.10	–0.23 ; 0.03	0.94
FS_{LF12}	0.86	0.87	–0.01	–0.10 ; 0.07	0.63
$FS_{LF18/LF12}$	0.77	0.85	–0.09	–0.17 ; 0.00	0.98
FS_{LF18}	0.67	0.75	–0.08	–0.19 ; 0.03	0.93
PS_{LF18}	0.40	0.50	–0.12	–0.24 ; -0.01	0.98

D=Posterior mean of differences between treated and untreated females, $HPD_{95\%}$=Highest posterior density region of the difference at 95%, P=Probability of the difference being lower than zero.

Table 4: Mean of the posterior distribution for treated and untreated females and features of the marginal posterior distributions of the differences between treated and untreated females in live foetus weight (LFWm, g), live foetus placental weight (LFPWm, g), and dead foetus placental weight (DFPWm, g) at 18 d of gestation.

Trait	Treated	Untreated	D	$HPD_{95\%}$	P
LFWm	2.00	1.93	0.03	–0.17 ; 0.23	0.62
LFPWm	2.48	2.23	0.25	0.01 ; 0.45	0.98
DFPWm	0.83	0.61	0.21	–0.08 ; 0.46	0.93

D=Posterior mean of differences between treated and untreated females, $HPD_{95\%}$=Highest posterior density region of the difference at 95%, *P*=Probability of the difference being higher than zero.

In agreement with these results obtained in rabbits, most prenatal mortality occurred during the early foetal period in an experiment of selection for ovulation rate in pigs (Freking *et al.,* 2007). In females with high ovulation rate, foetal mortality could be due to competition among foetuses for uterine space and resources (Adams, 1960a, b, Hafez, 1969 and Argente *et al.* 2008, in rabbits; Geisert and Schmitt, 2002 in pigs). However, no difference in IE between treated and untreated females was found, thus higher foetal mortality in treated females cannot be attributed to higher competition among foetuses. Both oocyte quality and embryo development variability can also affect foetal survival. It has been shown that low quality embryos and lesser developed embryos can be implanted, although they will probably die later (Wintenberger-Torres *et al.,* 1974 in rabbits; Pope, 1988; Wilde *et al.,* 1988 in pigs).

Placenta and foetus weight

Table 4 shows features of the estimated marginal posterior distributions of the differences between treated and untreated females for weights of foetuses and their placentas, used to assess the influence of a high ovulation rate on foetal and placental development at 18 d of gestation. For weight of live foetuses, we found no differences between treated and untreated females, although the estimation had a low accuracy (see high $HPD_{95\%}$, Table 4). Unexpectedly, foetal placenta weight of live foetuses in the treated females was heavier than in untreated ones (D=0.25 g; *P*=0.98). A similar result was obtained for foetal placenta weight of dead foetuses. In rabbits, Argente *et al.* (2008) observed that each additional foetus implied a decrease in the blood flow that reached each foetus, reducing foetal and placental weight. Thus, higher placenta weight could be associated with a lower number of developed foetuses in treated females between d 12 and 18 of gestation (D=–0.70 and –1.21 foetus for LF_{12} and LF_{18}, respectively); however, estimated differences for LFPWm and DFPWm were similar when LF_{18} was included as a covariate (data not shown).

Features of the estimated marginal posterior distributions of the differences between treated and untreated females for the variability in weights of live foetuses and their foetal placentas are shown in Table 5. Treated females showed a lower variability than untreated females for weights of live foetuses (D=–0.02 g; *P*=0.72) and foetal placenta (D=–0.05 g; *P*= 0.83). The lower observed variability for LFWv and LFPWv in the treated females seems not to be related to the lower number of foetuses at 18 d of gestation, as similar results were obtained when LF_{18} was included as a covariate (data not shown). In short, treated females showed similar foetus weight and higher foetal placenta weight to untreated females but lower variability for these traits. These results seem not to be related to a lower number of implanted embryos or number of live foetuses at 18 d of gestation.

Table 5: Mean of the posterior distribution for treated and untreated females and features of the marginal posterior distributions of the differences between treated and untreated females in the variability on live foetus weight (LFWv, g) and variability on live foetus placental weight (LFPWv, g) at 18 d of gestation.

Trait	Treated	Untreated	D	$HPD_{95\%}$	*P*
LFWv	0.22	0.24	-0.02	–0.07 ; 0.02	0.72
LFPWv	0.38	0.43	-0.05	–0.12 ; 0.02	0.83

D=Posterior mean of differences between treated and untreated females, $HPD_{95\%}$=Highest posterior density region of the difference at 95%, *P*=Probability of the difference being lower than zero.

In conclusion, a low increase in ovulation rate by hormonal treatment could be a good model to assess consequences on embryo and foetal survival rates due to increased ovulation rate by selection. The effect of increasing by three ova in rabbits leads to a lower embryo and foetal survival. Most foetal mortality occurs shortly after 12 d of gestation, and cannot be attributed to competition among foetuses, as no effects of number of implanted embryos and foetal weight were found.

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